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(54) Title: ANTIBIOTICS AND PROCESS FOR PREPARATION (57) Abstract A group of reagents, as diisocyanates, dianhydrides, diacidchlorides, diepoxides, carbodiimides and the like are utilized to link a wide variety of antibiotic moieties, reacted two at a time with said reagents, the said antibiotic moieties containing groups reactive with the linking reagents as carboxylic acid, alcohol, primary amine, and secondary amine functional groups, said functional groups being present as singularities or as multiplicities, products being readily purified using chromatographic techniques, and said products of above reactions being valuable for the treatment of microbial infections of man and animals.		

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ANTIBIOTICS AND PROCESS FOR PREPARATION

FIELD OF THE INVENTION

This invention is concerned with the preparation of a wide variety of antibiotics of new and novel structure and antimicrobial activity. The compounds thus prepared are products from the linking of diverse antibiotic moieties via difunctional organic compounds such as diisocyanates, dianhydrides, diacidchlorides, diepoxides and carbodiimides, said antibiotics being drawn from the classes of compounds sulfonamides, penicillins and related, cephalosporins and related, quinolones, chloramphenicol, erythromycins, metronidazole, tetracyclines and aminoglycocides.

BACKGROUND OF THE INVENTION

The medical literature regarding antimicrobial agents is vast and describes a number of antimicrobials including naturally occurring compounds as well as synthetic or semisynthetic compounds produced in the organic laboratory. These antimicrobial agents are classified as noted above, and there are many classes in addition to the above-noted ones.

It has been realized that the linking of two antibiotic moieties functioning in different fashions, as for example inhibiting cell-wall synthesis or protein synthesis or DNA synthesis, can be of value. Two antibiotic moieties can also be linked in which one is known to attack Gram positive bacteria and another to attack Gram negative bacteria, and this new entity is of value.

Usually the synthesis of linked antibiotics requires an extended set of organic laboratory procedures in which prior to the linkage of diverse types, such as quinolones and lactams, certain groups in the molecule must be blocked, the blocked entity then linked to a second antibiotic, which may also require blocking of some functional groups, and also the blocking groups require removal. It has been found surprisingly that a number of difunctional reagents can effect an efficient linkage of very diverse antibiotic structures. Further, the progress of the reaction can easily be followed via IR spectroscopy techniques, and the isolation of meaningful quantities achieved in facile fashion via liquid chromatography techniques.

SUMMARY OF THE INVENTION

This invention is concerned with simple methods of preparing a large number of new and novel structures possessing a wide range of antibiotic activity via linking together two antibiotic moieties.

A - L - B

wherein A has the structure drawn from the following classes of antibiotics:

1. sulfonamides and related
2. penicillins and related
3. cephalosporins and related
4. quinolones
5. chloramphenicol
6. erythromycin
7. metronidazole
8. tetracyclines
9. aminoglycosides

and B, drawn from the same classes.

The classes may be further characterized by the following general formulas and particular examples. L is drawn from a group of difunctional linking reagents.

1. Sulfonamides and Related

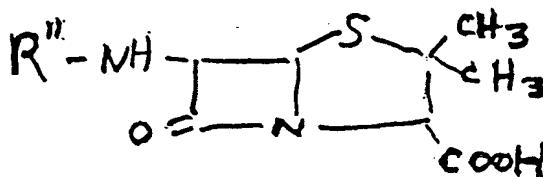


where R' is a variety of substituents.

The sulfonamides listed below are of particular interest:

- A. p-aminobenzenesulfonamide
- B. sulfamethoxyazole
- C. acetylsulfoxazole
- D. sulfamethoxypyridazine
- E. sulfadiazine

2. Penicillins and Related

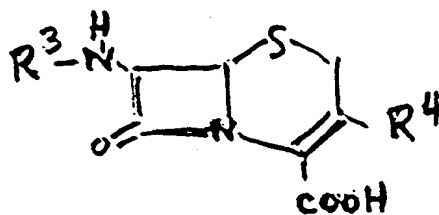


where R'' is a variety of substituents. The penicillins listed below are of particular interest.

- A. benzyl penicillin
- B. procaine penicillin G
- C. phenoxymethyl penicillin
- D. ampicillin
- E. amoxycillin

- F. methicillin
- G. oxacillin
- H. cloxacillin
- I. dicloxacillin
- J. flucloxacillin
- K. nafcillin
- L. carbenicillin
- M. ticarcillin
- N. talampicillin
- O. becampicillin
- P. pivampicillin
- Q. penamcarboxylic acid
- R. hydroxyethyl penem
- S. imipenem
- T. amdinocilin

3. Cephalosporins and Related:

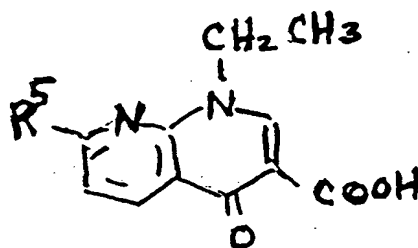


where R^3 and R^4 are a variety of substituents. The cephalosporins listed below are of particular interest.

- A. cephalosporin C
- B. cephalothin
- C. cephaloridine

- D. cephradine
- E. cephalolin
- F. cephalixin
- G. cefadroxil
- H. cefaclor
- I. cephamandole
- J. cefuroxime
- K. cefotaxime
- L. ceftizoxime
- M. ceftazidime
- N. cefoperazone
- O. cephamycin C
- P. cefoxitin
- Q. moxalactam

4. Quinolones

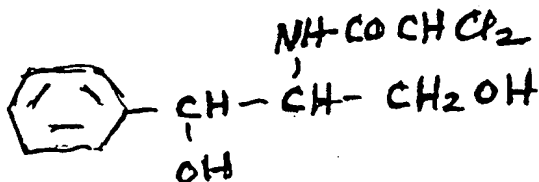


where R⁵ is a variety of substituents and the quinoline nucleus contains fluoro atom substitution. The quinolones listed below are of particular interest.

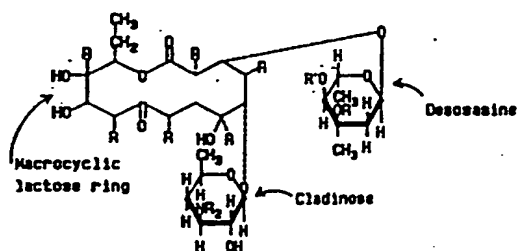
- A. nalidixic acid
- B. norfloxacin

- C. enoxacin
- D. ciprofloxacin
- E. ofloxacin

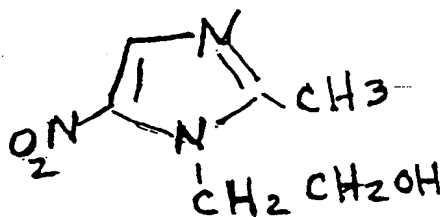
5. Chloramphenicol



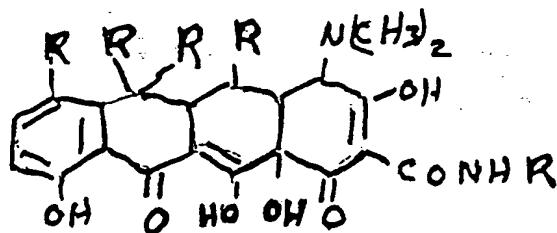
6. Erythromycin



7. Metronidazole



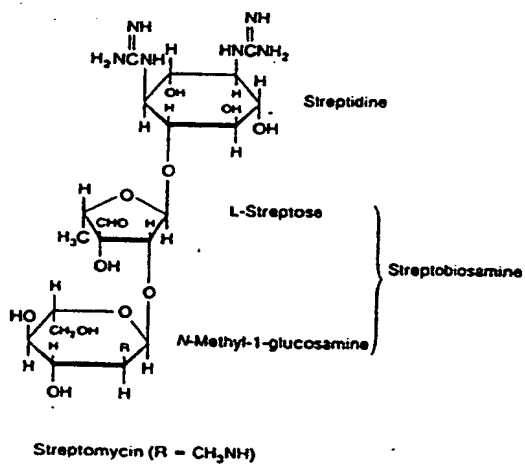
8. Tetracyclines



where the general formula given above is substituted to yield the particular compounds listed below.

- A. tetracycline
- B. oxytetracycline
- C. chlortetracycline
- D. rolitetracycline
- E. methacycline
- F. doxycycline
- G. demeclocycline
- H. sancycline
- I. lymecycline
- J. clomocycline
- K. minocycline

9. Aminoglycosides



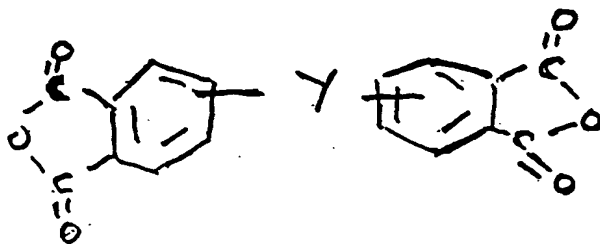
The general formula above is variously substituted to give the particular isomers listed below.

- A. streptomycin
- B. tobramycin
- C. kanamycin
- D. amikacin
- E. gentamicin C1
- F. nitilimicin
- G. neomycin
- H. paromomycin
- I. spectinomycin

The linking reagents are drawn from the type listed below.

Diisocyanates $\text{NCO} - \text{Y} - \text{NCO}$

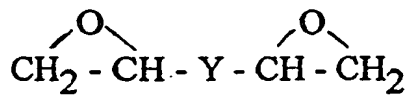
Dianhydrides



Diacidchlorides



Diepoxides



Carbodiimides



In the above general formulas Y can be aliphatic, alicyclic, aromatic and heterocyclic groups.

The particular formulas for each type are listed below.

Diisocyanates:

1,6-hexamethylenediisocyanate
2,4-tolyldiisocyanate
2,6-tolyldiisocyanate
4,4'-methylene bis phenylisocyanate
4,4'-isopropylidene bis phenylisocyanate
1,4-phenyldiisothiocyanate
1,4-phenyldiisocyanate

Dianhydrides

pyromellitic dianhydride
bis maleic dianhydride
3,3,4,4'-benzophenonetetracarboxylic dianhydride
1,2,6,7- hexanetetracarboxylic dianhydride
1,2,4,5- naphthalenetetracarboxylic dianhydride

Diacidchlorides

terphthaloyl chloride
isophthaloyl chloride
phthaloyl chloride
adipoyl chloride
glutaryl chloride

Diepoxides

1,3-butane diepoxide
1,5-cyclooctatetraene diepoxide
vinylcyclohexene diepoxide
1,4-divinylbenzene diepoxide

Carbodiimides

dicyclohexylcarbodiimide
ditolylcarbodiimide

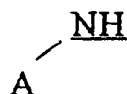
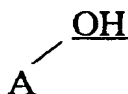
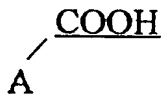
Rules Based on Linking Agents

Surprisingly only a few rules must be obeyed to take advantage of five different linking reagents applicable to linking two antibiotic molecules. The five linking reagents are: diisocyanates, dianhydrides, diacidchlorides, diepoxides and carbodiimides.

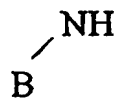
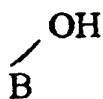
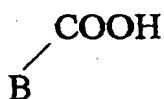
The types of antibiotics that can be linked are sulfonamides, trimethoprim, penicillins and related structures, cephalosporins and related structures, chloramphenicol, erythromycin, metronidazole, quinolones, tetracyclines and aminoglycosides.

The linking rules are as follows:

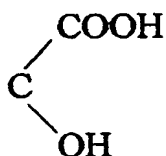
1. Diisocyanates can react with all acid groups, all hydroxyl groups and all primary and secondary amino groups. Thus any antibiotic moiety, A, containing a carboxylic acid, hydroxyl or amine function



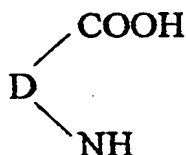
can be linked to any other antibiotic moiety B containing a carboxylic acid, hydroxyl or amine function.



When a single antibiotic moiety contains more than a single functional group, as C,



the diisocyanate can be used to link with an antibiotic moiety containing a single reactive group, as A and B above, or with an antibiotic moiety containing two functional groups as D, carboxylic acid and amine.



When a diisocyanate is used to link antibiotic moieties containing a plurality of groups, a mixture of products will be realized, but with chromatographic techniques the mixtures are easily separated.

Summarizing, the diisocyanate can be used to link any two antibiotics containing at least one carboxylic acid, alcohol or amino functional group, and will also effect linkage when each antibiotic moiety contains a plurality of groups.

2. Dianhydrides can be employed to link a wide variety of antibiotic moieties containing hydroxy or primary or secondary amines. The reagent will also link antibiotic molecules where each antibiotic moiety contains a plurality of hydroxy, primary and secondary amine functional groups.
3. Diacidchlorides can be employed to link a wide variety of antibiotic moieties containing hydroxyl and primary or secondary amine functional groups, and also where each moiety contains a plurality of said functions.
4. Diepoxides can be utilized to link a very wide variety of antibiotic moieties where each contains carboxylic acid, alcohol, and primary or secondary amine functional groups, or a plurality of such groups.
5. Carbodiimides can be utilized to link a wide variety of antibiotic moieties where each moiety contains at least one of the following functional groups: carboxylic acid, alcohol, and primary or secondary amine. This reagent differs from the four previously discussed since the reagent bonds the two antibiotic moieties via the removal of the elements of water from the functional groups. Moieties containing carboxylic acid groups can be linked with moieties containing carboxylic acid groups to form anhydrides. Moieties containing carboxylic acid groups can be linked to moieties containing alcohols or primary or secondary amines to form esters or amides. Moieties containing hydroxyl groups can be linked to moieties containing hydroxyl or primary or secondary amine groups to form ethers or

substituted amines. Where pluralities of the carboxylic acid, hydroxyl or amine functional groups are contained in one or both antibiotic moieties, linkage will occur but the products may be complex and require chromatographic separation.

DESCRIPTION OF THE INVENTION

Section 1

The present invention describes methods for making a number of linked antibiotic molecules. The linked antibiotics are to be utilized in treating various infections in man and animals, without undue adverse side effects such as toxicity, inflammation and allergies.

There are several groups of these to-be linked compounds which can be enumerated: sulfonamides, penicillins, cephalosporins, quinolones, chloramphenicol, erythromycin, metronidazole, tetracyclines and aminoglycosides. With each case, the antibiotics to be linked will be taken two at a time from the above groups, thus:

sulfonamide + sulfonamide

sulfonamide + penicillin

sulfonamide + cephalosporin

sulfonamide + quinolone

sulfonamide + chloramphenicol

sulfonamide + erythromycin

sulfonamide + metronidazole

sulfonamide + tetracycline

sulfonamide + aminoglycoside

penicillin + penicillin

penicillin + cephalosporin

penicillin + quinolones

penicillin + chloramphenicol

penicillin + erythromycin
penicillin + metronidazole
penicillin + tetracyclines
penicillin + aminoglycosides

cephalosporin + cephalosporin
cephalosporin + quinolone
cephalosporin + chloramphenicol
cephalosporin + erythromycin
cephalosporin + metronidazole
cephalosporin + tetracyclines
cephalosporin + aminoglycoside

quinolone + quinolone
quinolone + chloramphenicol
quinolone + erythromycin
quinolone + metronidazole
quinolone + tetracyclines
quinolone + aminoglycoside

chloramphenicol + chloramphenicol
chloramphenicol + erythromycin
chloramphenicol + metronidazole
chloramphenicol + tetracyclines
chloramphenicol + aminoglycoside

erythromycin + erythromycin
erythromycin + metronidazole
erythromycin + tetracyclines
erythromycin + aminoglycoside

metronidazole + metronidazole
metronidazole + tetracyclines
metronidazole + aminoglycoside

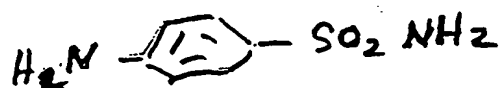
tetracyclines + tetracyclines
tetracyclines + aminoglycosides

aminoglycoside + aminoglycoside

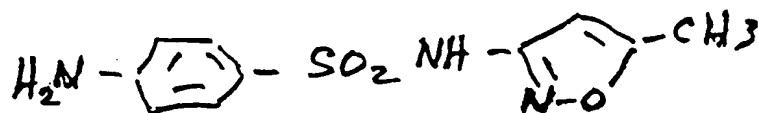
Within each of the above groups of antibiotics the members of each to be linked are defined as:

1. Sulfonamides:

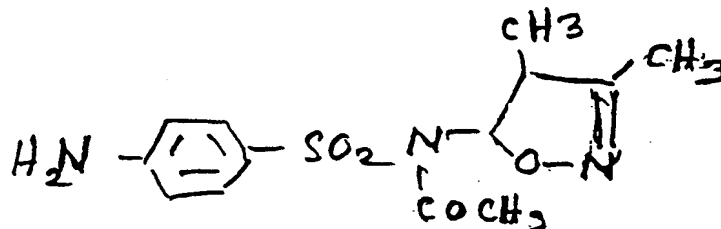
A. p-aminobenzenesulfonamide



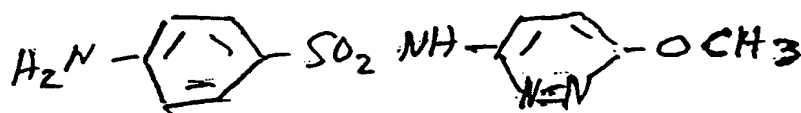
B. sulfamethoxyazole



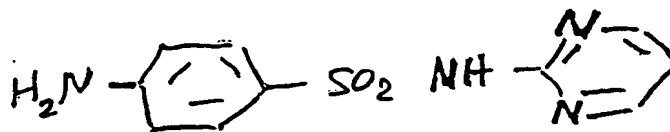
C. acetylsulfoxazole



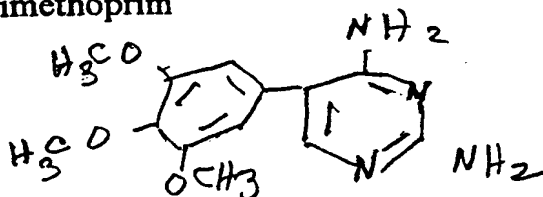
D. sulfamethoxypyridazine



E. sulfadiazine

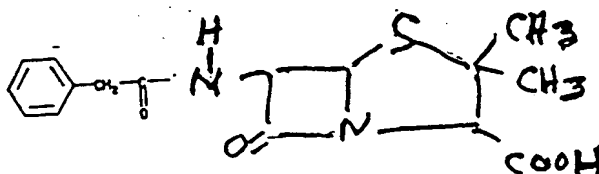


F. trimethoprim

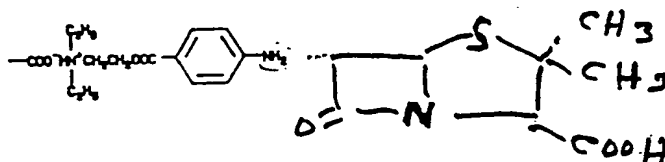


2. Penicillins:

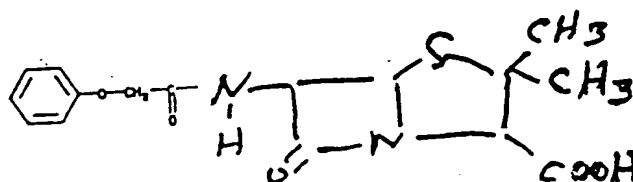
A. benzyl penicillin



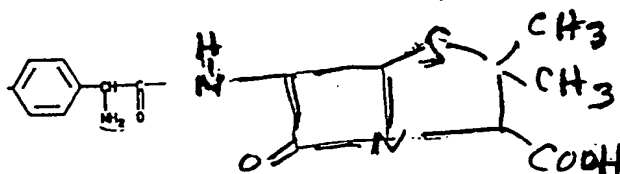
B. procaine penicillin G



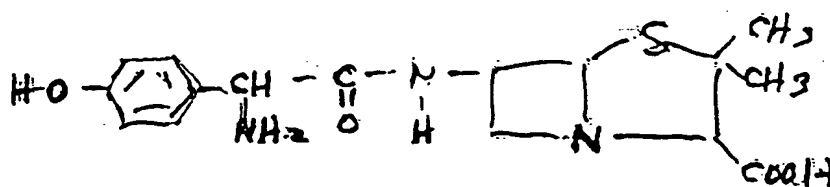
C. phenoxymethyl penicillin



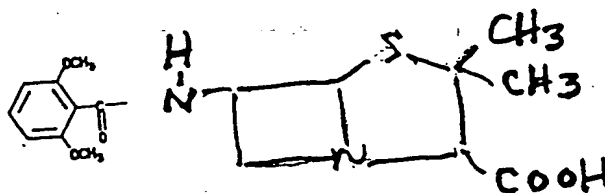
D. ampicillin



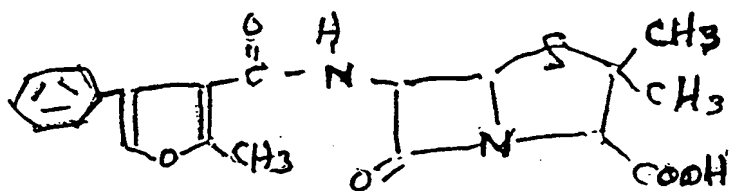
E. amoxycillin



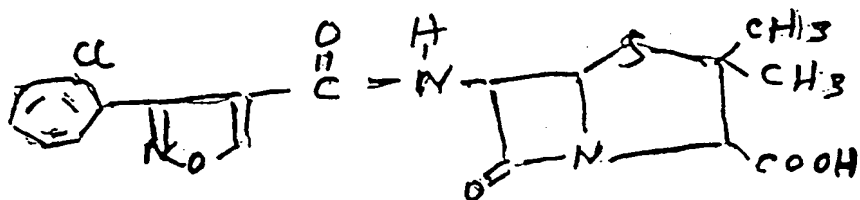
F. methicillin



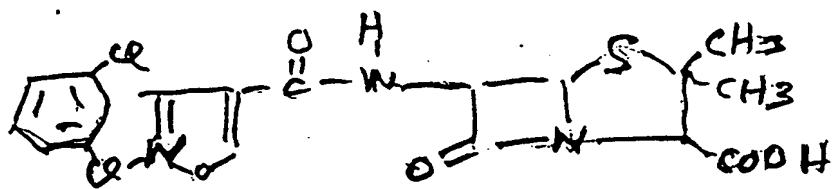
G. oxacillin



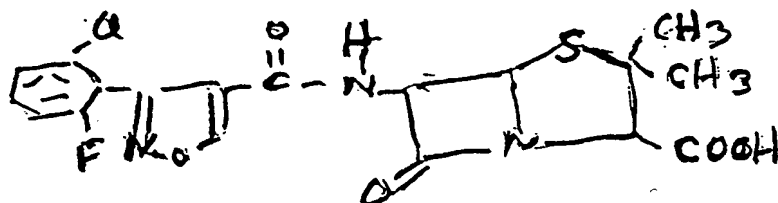
H. cloxacillin



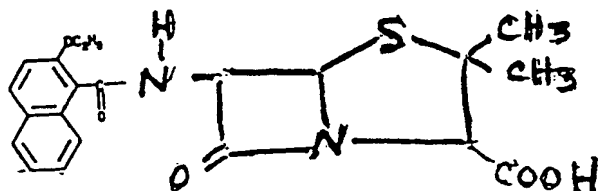
I. dicloxacillin



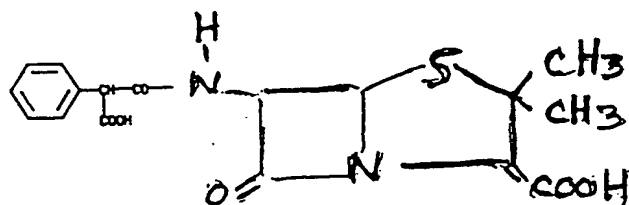
J. flucloxacillin



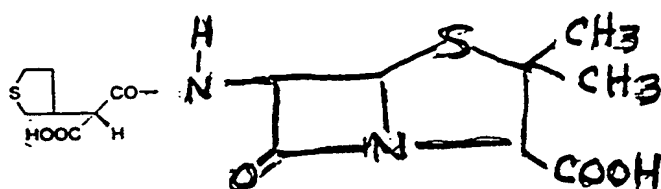
K. nafcillin



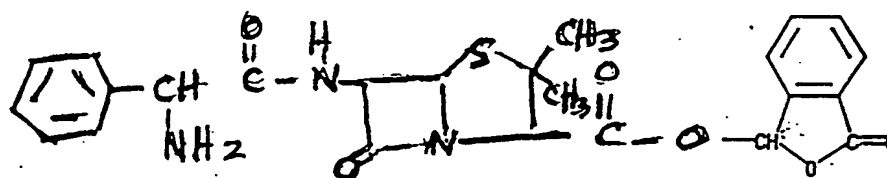
L. carbenicillin



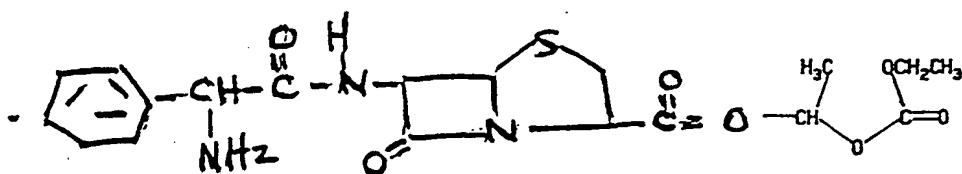
M. ticarcillin



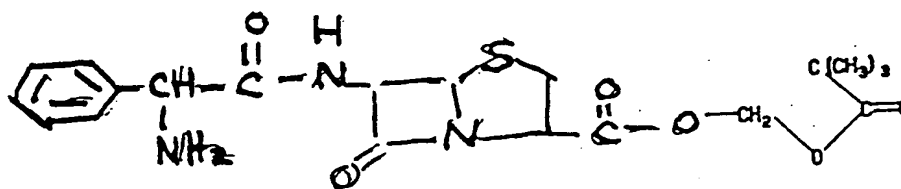
N. talampicillin



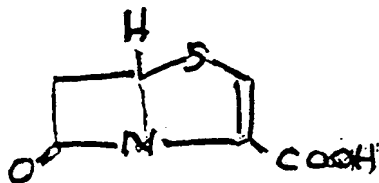
O. becampicillin



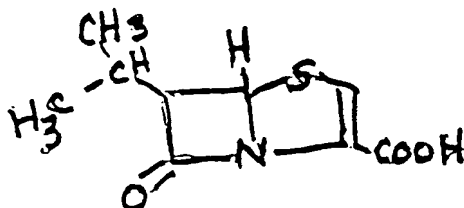
P. pivampicillin



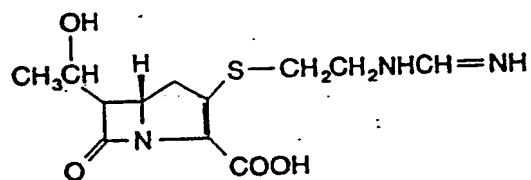
Q. penemcarboxylic acid



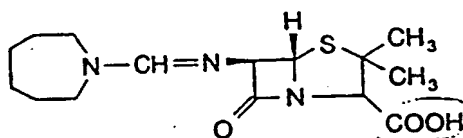
R. hydroxyethyl penem



S. imipenem

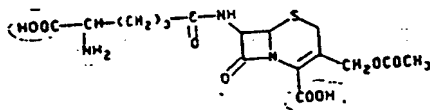


T. amdinocilin

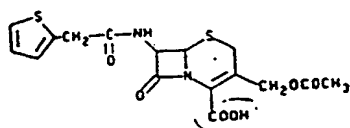


3. Cephalosporins:

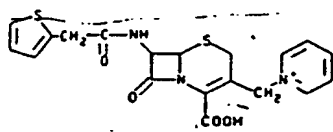
A. cephalosporin C



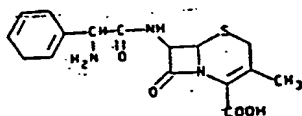
B. cephalothin



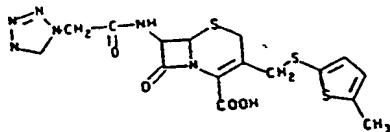
C. cephaloridine



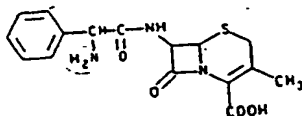
D. cephradine



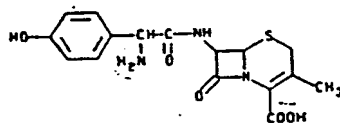
E. cephazolin



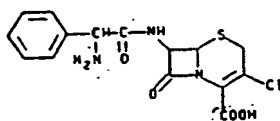
F. cephalexin



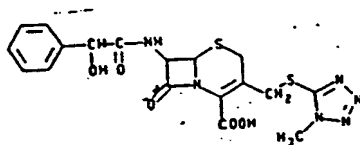
G. cefadroxil



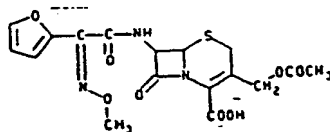
H. cefaclor



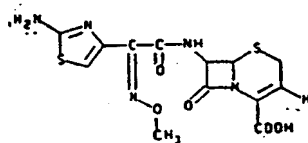
I. cephamandole



J. cefuroxime

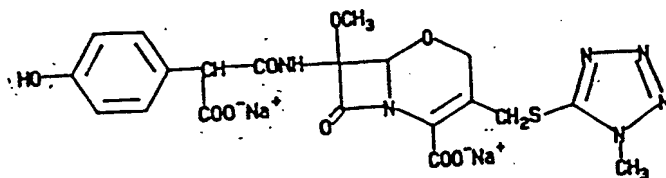


K. cefotaxime



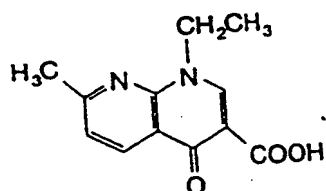
CN1C(=O)N(C(=O)N2C(=O)N(C(=O)N2C(=O)O)C(=O)O)C(=O)N3C(=O)N(C(=O)N3C(=O)O)C(=O)ONC1=CC=C(S1)C(=O)N[C@@H](C(=O)O)C2=CC=C(C=C2)C(=O)N[C@@H](C(=O)O)C3=CC=C(C=C3)C(=O)N[C@@H](C(=O)O)C4=CC=C(C=C4)C(=O)N[C@@H](C(=O)O)C5=CC=C(C=C5)C(=O)N[C@@H](C(=O)O)C6=CC=C(C=C6)C(=O)N[C@@H](C(=O)O)C7=CC=C(C=C7)C(=O)N[C@@H](C(=O)O)C8=CC=C(C=C8)C(=O)N[C@@H](C(=O)O)C9=CC=C(C=C9)C(=O)N[C@@H](C(=O)O)C10=CC=C(C=C10)C(=O)N[C@@H](C(=O)O)C11=CC=C(C=C11)C(=O)N[C@@H](C(=O)O)C12=CC=C(C=C12)C(=O)N[C@@H](C(=O)O)C13=CC=C(C=C13)C(=O)N[C@@H](C(=O)O)C14=CC=C(C=C14)C(=O)N[C@@H](C(=O)O)C15=CC=C(C=C15)C(=O)N[C@@H](C(=O)O)C16=CC=C(C=C16)C(=O)N[C@@H](C(=O)O)C17=CC=C(C=C17)C(=O)N[C@@H](C(=O)O)C18=CC=C(C=C18)C(=O)N[C@@H](C(=O)O)C19=CC=C(C=C19)C(=O)N[C@@H](C(=O)O)C20=CC=C(C=C20)C(=O)N[C@@H](C(=O)O)C21=CC=C(C=C21)C(=O)N[C@@H](C(=O)O)C22=CC=C(C=C22)C(=O)N[C@@H](C(=O)O)C23=CC=C(C=C23)C(=O)N[C@@H](C(=O)O)C24=CC=C(C=C24)C(=O)N[C@@H](C(=O)O)C25=CC=C(C=C25)C(=O)N[C@@H](C(=O)O)C26=CC=C(C=C26)C(=O)N[C@@H](C(=O)O)C27=CC=C(C=C27)C(=O)N[C@@H](C(=O)O)C28=CC=C(C=C28)C(=O)N[C@@H](C(=O)O)C29=CC=C(C=C29)C(=O)N[C@@H](C(=O)O)C30=CC=C(C=C30)C(=O)N[C@@H](C(=O)O)C31=CC=C(C=C31)C(=O)N[C@@H](C(=O)O)C32=CC=C(C=C32)C(=O)N[C@@H](C(=O)O)C33=CC=C(C=C33)C(=O)N[C@@H](C(=O)O)C34=CC=C(C=C34)C(=O)N[C@@H](C(=O)O)C35=CC=C(C=C35)C(=O)N[C@@H](C(=O)O)C36=CC=C(C=C36)C(=O)N[C@@H](C(=O)O)C37=CC=C(C=C37)C(=O)N[C@@H](C(=O)O)C38=CC=C(C=C38)C(=O)N[C@@H](C(=O)O)C39=CC=C(C=C39)C(=O)N[C@@H](C(=O)O)C40=CC=C(C=C40)C(=O)N[C@@H](C(=O)O)C41=CC=C(C=C41)C(=O)N[C@@H](C(=O)O)C42=CC=C(C=C42)C(=O)N[C@@H](C(=O)O)C43=CC=C(C=C43)C(=O)N[C@@H](C(=O)O)C44=CC=C(C=C44)C(=O)N[C@@H](C(=O)O)C45=CC=C(C=C45)C(=O)N[C@@H](C(=O)O)C46=CC=C(C=C46)C(=O)N[C@@H](C(=O)O)C47=CC=C(C=C47)C(=O)N[C@@H](C(=O)O)C48=CC=C(C=C48)C(=O)N[C@@H](C(=O)O)C49=CC=C(C=C49)C(=O)N[C@@H](C(=O)O)C50=CC=C(C=C50)C(=O)N[C@@H](C(=O)O)C51=CC=C(C=C51)C(=O)N[C@@H](C(=O)O)C52=CC=C(C=C52)C(=O)N[C@@H](C(=O)O)C53=CC=C(C=C53)C(=O)N[C@@H](C(=O)O)C54=CC=C(C=C54)C(=O)N[C@@H](C(=O)O)C55=CC=C(C=C55)C(=O)N[C@@H](C(=O)O)C56=CC=C(C=C56)C(=O)N[C@@H](C(=O)O)C57=CC=C(C=C57)C(=O)N[C@@H](C(=O)O)C58=CC=C(C=C58)C(=O)N[C@@H](C(=O)O)C59=CC=C(C=C59)C(=O)N[C@@H](C(=O)O)C60=CC=C(C=C60)C(=O)N[C@@H](C(=O)O)C61=CC=C(C=C61)C(=O)N[C@@H](C(=O)O)C62=CC=C(C=C62)C(=O)N[C@@H](C(=O)O)C63=CC=C(C=C63)C(=O)N[C@@H](C(=O)O)C64=CC=C(C=C64)C(=O)N[C@@H](C(=O)O)C65=CC=C(C=C65)C(=O)N[C@@H](C(=O)O)C66=CC=C(C=C66)C(=O)N[C@@H](C(=O)O)C67=CC=C(C=C67)C(=O)N[C@@H](C(=O)O)C68=CC=C(C=C68)C(=O)N[C@@H](C(=O)O)C69=CC=C(C=C69)C(=O)N[C@@H](C(=O)O)C70=CC=C(C=C70)C(=O)N[C@@H](C(=O)O)C71=CC=C(C=C71)C(=O)N[C@@H](C(=O)O)C72=CC=C(C=C72)C(=O)N[C@@H](C(=O)O)C73=CC=C(C=C73)C(=O)N[C@@H](C(=O)O)C74=CC=C(C=C74)C(=O)N[C@@H](C(=O)O)C75=CC=C(C=C75)C(=O)N[C@@H](C(=O)O)C76=CC=C(C=C76)C(=O)N[C@@H](C(=O)O)C77=CC=C(C=C77)C(=O)N[C@@H](C(=O)O)C78=CC=C(C=C78)C(=O)N[C@@H](C(=O)O)C79=CC=C(C=C79)C(=O)N[C@@H](C(=O)O)C80=CC=C(C=C80)C(=O)N[C@@H](C(=O)O)C81=CC=C(C=C81)C(=O)N[C@@H](C(=O)O)C82=CC=C(C=C82)C(=O)N[C@@H](C(=O)O)C83=CC=C(C=C83)C(=O)N[C@@H](C(=O)O)C84=CC=C(C=C84)C(=O)N[C@@H](C(=O)O)C85=CC=C(C=C85)C(=O)N[C@@H](C(=O)O)C86=CC=C(C=C86)C(=O)N[C@@H](C(=O)O)C87=CC=C(C=C87)C(=O)N[C@@H](C(=O)O)C88=CC=C(C=C88)C(=O)N[C@@H](C(=O)O)C89=CC=C(C=C89)C(=O)N[C@@H](C(=O)O)C90=CC=C(C=C90)C(=O)N[C@@H](C(=O)O)C91=CC=C(C=C91)C(=O)N[C@@H](C(=O)O)C92=CC=C(C=C92)C(=O)N[C@@H](C(=O)O)C93=CC=C(C=C93)C(=O)N[C@@H](C(=O)O)C94=CC=C(C=C94)C(=O)N[C@@H](C(=O)O)C95=CC=C(C=C95)C(=O)N[C@@H](C(=O)O)C96=CC=C(C=C96)C(=O)N[C@@H](C(=O)O)C97=CC=C(C=C97)C(=O)N[C@@H](C(=O)O)C98=CC=C(C=C98)C(=O)N[C@@H](C(=O)O)C99=CC=C(C=C99)C(=O)N[C@@H](C(=O)O)C100=CC=C(C=C100)C(=O)N[C@@H](C(=O)O)C101=CC=C(C=C101)C(=O)N[C@@H](C(=O)O)C102=CC=C(C=C102)C(=O)N[C@@H](C(=O)O)C103=CC=C(C=C103)C(=O)N[C@@H](C(=O)O)C104=CC=C(C=C104)C(=O)N[C@@H](C(=O)O)C105=CC=C(C=C105)C(=O)N[C@@H](C(=O)O)C106=CC=C(C=C106)C(=O)N[C@@H](C(=O)O)C107=CC=C(C=C107)C(=O)N[C@@H](C(=O)O)C108=CC=C(C=C108)C(=O)N[C@@H](C(=O)O)C109=CC=C(C=C109)C(=O)N[C@@H](C(=O)O)C110=CC=C(C=C110)C(=O)N[C@@H](C(=O)O)C111=CC=C(C=C111)C(=O)N[C@@H](C(=O)O)C112=CC=C(C=C112)C(=O)N[C@@H](C(=O)O)C113=CC=C(C=C113)C(=O)N[C@@H](C(=O)O)C114=CC=C(C=C114)C(=O)N[C@@H](C(=O)O)C115=CC=C(C=C115)C(=O)N[C@@H](C(=O)O)C116=CC=C(C=C116)C(=O)N[C@@H](C(=O)O)C117=CC=C(C=C117)C(=O)N[C@@H](C(=O)O)C118=CC=C(C=C118)C(=O)N[C@@H](C(=O)O)C119=CC=C(C=C119)C(=O)N[C@@H](C(=O)O)C120=CC=C(C=C120)C(=O)N[C@@H](C(=O)O)C121=CC=C(C=C121)C(=O)N[C@@H](C(=O)O)C122=CC=C(C=C122)C(=O)N[C@@H](C(=O)O)C123=CC=C(C=C123)C(=O)N[C@@H](C(=O)O)C124=CC=C(C=C124)C(=O)N[C@@H](C(=O)O)C125=CC=C(C=C125)C(=O)N[C@@H](C(=O)O)C126=CC=C(C=C126)C(=O)N[C@@H](C(=O)O)C127=CC=C(C=C127)C(=O)N[C@@H](C(=O)O)C128=CC=C(C=C128)C(=O)N[C@@H](C(=O)O)C129=CC=C(C=C129)C(=O)N[C@@H](C(=O)O)C130=CC=C(C=C130)C(=O)N[C@@H](C(=O)O)C131=CC=C(C=C131)C(=O)N[C@@H](C(=O)O)C132=CC=C(C=C132)C(=O)N[C@@H](C(=O)O)C133=CC=C(C=C133)C(=O)N[C@@H](C(=O)O)C134=CC=C(C=C134)C(=O)N[C@@H](C(=O)O)C135=CC=C(C=C135)C(=O)N[C@@H](C(=O)O)C136=CC=C(C=C136)C(=O)N[C@@H](C(=O)O)C137=CC=C(C=C137)C(=O)N[C@@H](C(=O)O)C138=CC=C(C=C138)C(=O)N[C@@H](C(=O)O)C139=CC=C(C=C139)C(=O)N[C@@H](C(=O)O)C140=CC=C(C=C140)C(=O)N[C@@H](C(=O)O)C141=CC=C(C=C141)C(=O)N[C@@H](C(=O)O)C142=CC=C(C=C142)C(=O)N[C@@H](C(=O)O)C143=CC=C(C=C143)C(=O)N[C@@H](C(=O)O)C144=CC=C(C=C144)C(=O)N[CCCCC1=NC(=O)N(C1)C(=O)NCC(=O)Nc2ccc(O)cc2C(=O)Nc3csc4c(c3)C(=O)N4Cc5cnc(C)n5NC(CC(=O)O)CCCC(=O)N1C(=O)C2(C)SC(C(=O)O)=C(NC(=O)O)C2N1CCOC(=O)[C@@H]1C(=O)N2C(=O)C(=C[C@H]2S1)C(=O)O[C@H]3C=CC=C[C@@H]3S

Q. moxalactam

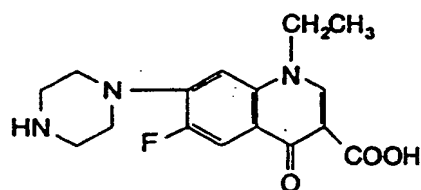


4. Quinolones:

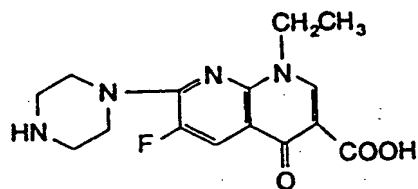
A. nalidixic acid



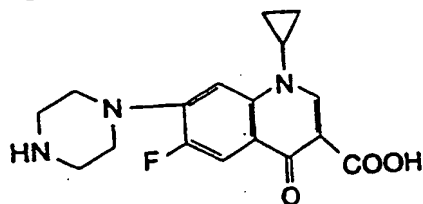
B. norfloxacin



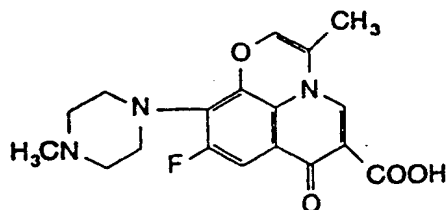
C. enoxacin



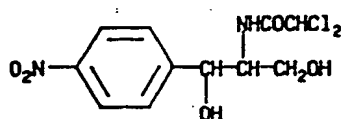
D. ciprofloxacin



E. ofloxacin

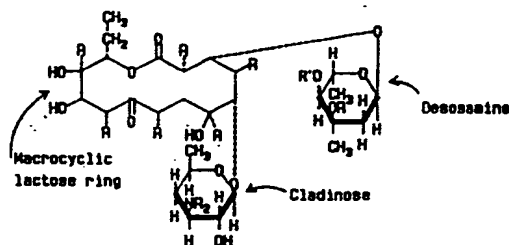


5. Chloramphenicol:

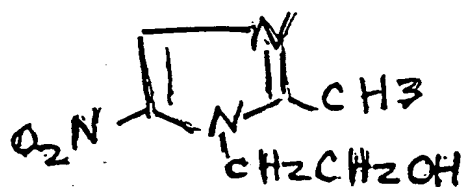


6. Erythromycin:

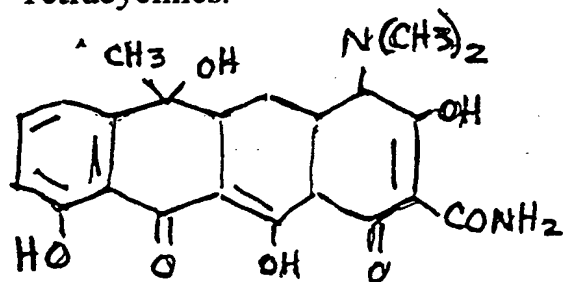
A. erythromycin



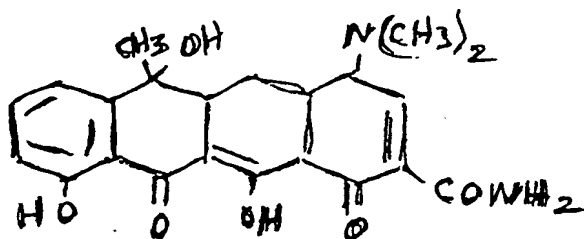
7. Metronidazole:



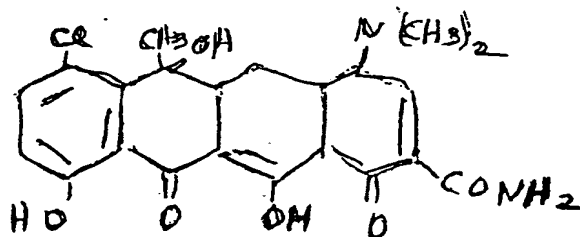
8. Tetracyclines:



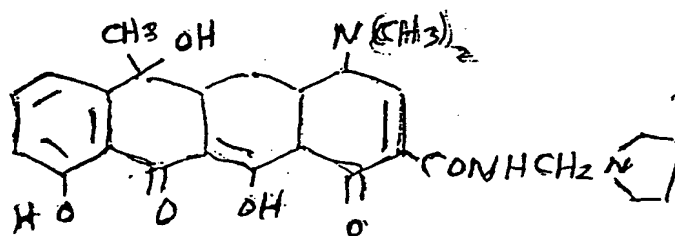
B. oxytetracycline



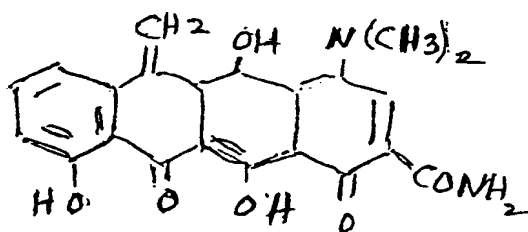
C. chlortetracycline



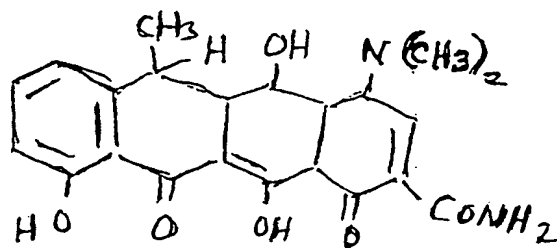
D. rolitetracycline



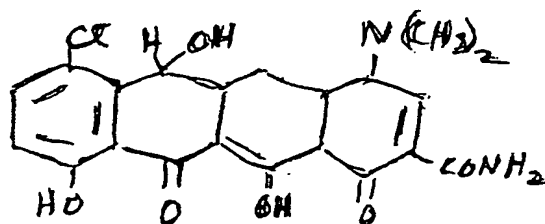
E. methacycline



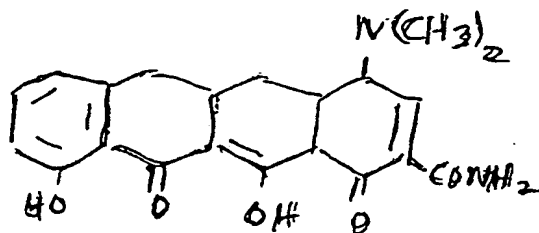
F. doxycycline



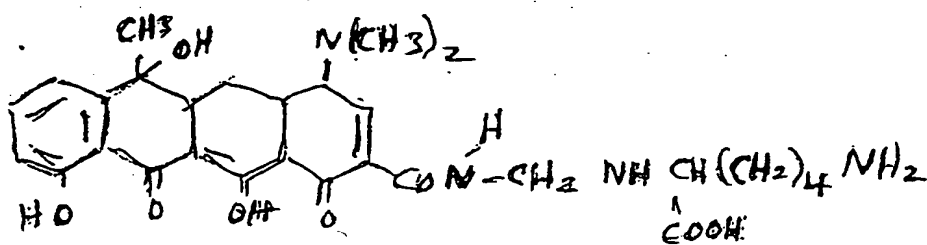
G. demeclocycline



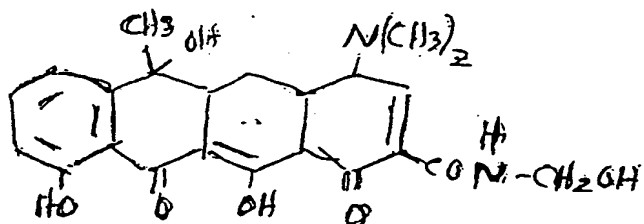
H. sancycline



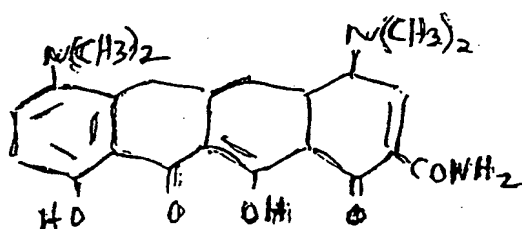
I. lymecycline



J. clomocycline

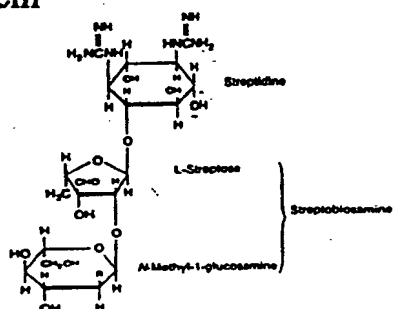


K. minocycline

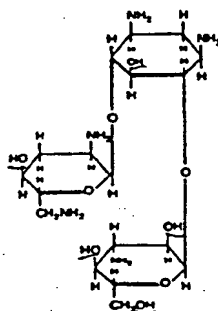


9. Aminoglycosides:

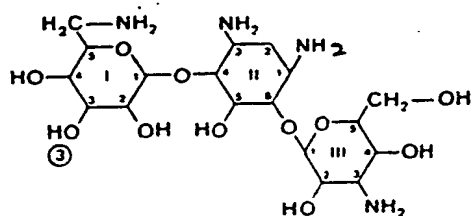
A. streptomycin



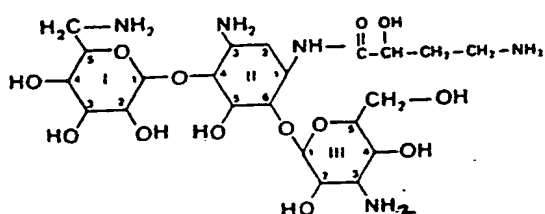
B. tobramycin



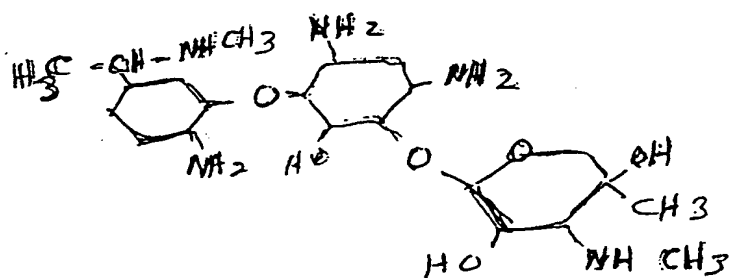
C. kanamycin



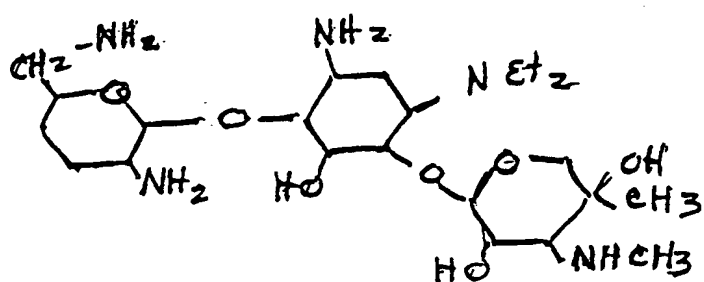
D. amikacin



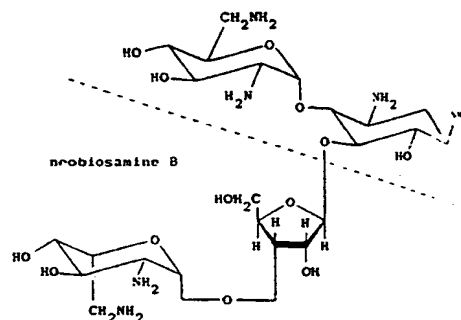
E. gentamicin Cl



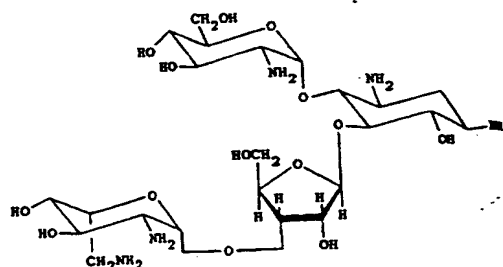
F. netilmicin



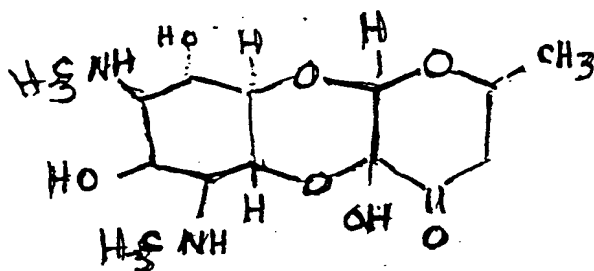
G. neomycin



H. paromomycin



I. spectinomycin



The linking agents that will be used to link the antibiotic moities are drawn from several classes of organic molecules:

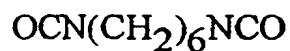
- I. Diisocyanates and related structures
- II. Dianhydrides
- III. Diacidchlorides
- IV. Diepoxides

V. Dicyclohexylcarbodiimide and related structures

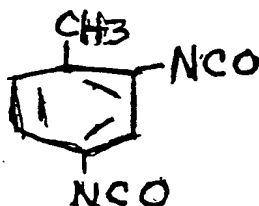
The class I linking agents are drawn from the group consisting of the following structures:

I. Diisocyanates and related structures:

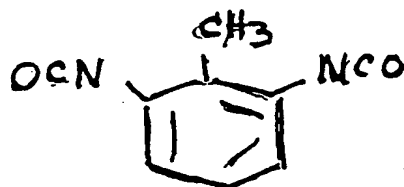
A. hexamethylene diisocyanate



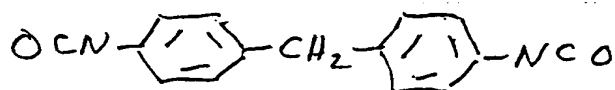
B. 2,4-tolyldiisocyanate



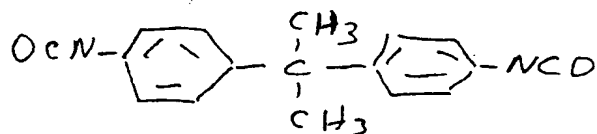
C. 2,6-tolyldiisocyanate



D. 4,4'-methylene-bis-phenylisocyanate



E. 4,4'-isopropylidene-bis-phenylisocyanate



F. 1,4-phenyldiisothiocyanate

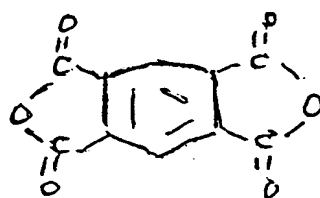


G. 1,4-phenyldissocyanate

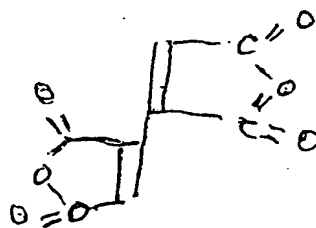


II. Dianhydrides:

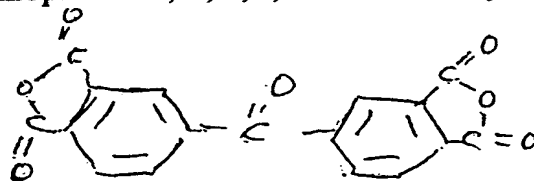
A. pyromellitic dianhydride



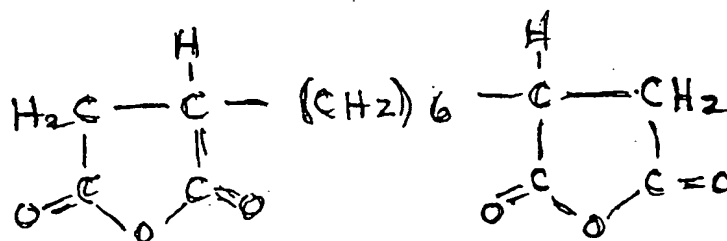
B. bismaleic dianhydride



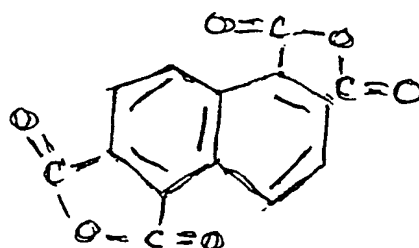
C. benzophenone, 3,3',4,4' tetracarboxylic anhydride



D. 1,2,6,7-hexane-tetracarboxylic anhydride



E. 1,2,5,6-naphthalene tetracarboxylic anhydride

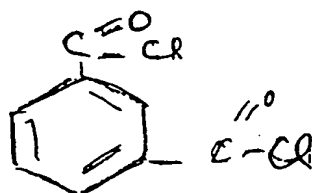


III. Diacidchlorides:

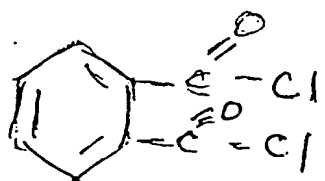
A. terphthaloyl dichloride



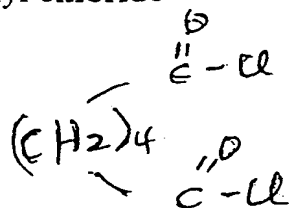
B. isophthaloyl dichloride



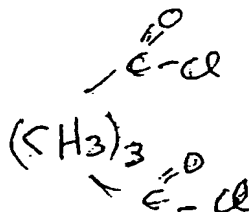
C. phthaloyl dichloride



D. adipoyl chloride

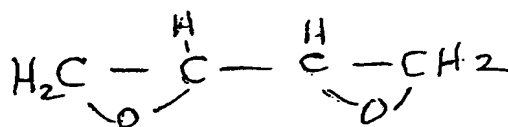


E. glutaryl chloride

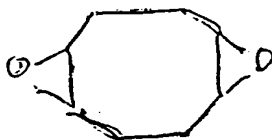


IV. Diepoxides and related structures:

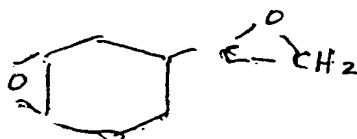
A. 1,3-butadiene diepoxide



B. cyclooctatetraene diepoxide, 1.5



C. vinyl cyclohexene

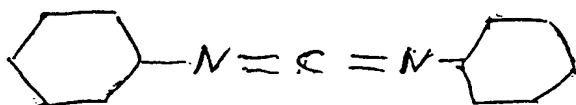


D. divinylbenzene epoxide

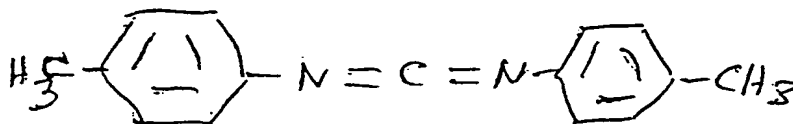


V. Carbodiimides and related structures:

A. Dicyclohexylcarbodiimide



B. Ditolylcarbodiimide



DESCRIPTION OF THE INVENTION

Section 2

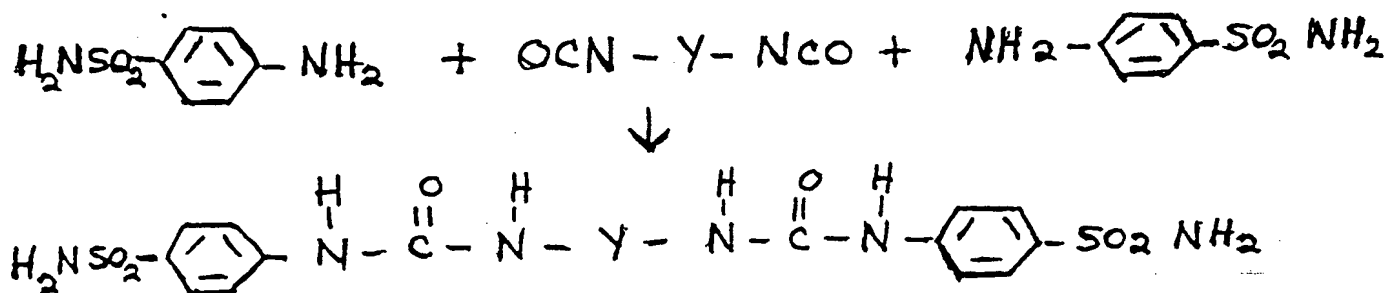
Methods of Linking Antibiotic Moieties:

The structure of the two antibiotic moieties being linked will determine the nature of the particular linking agent to be employed. Thus when sulfonamides listed above are to be coupled the basic sulfonamide structure below shows that the group which will be linking the two sulfonamide

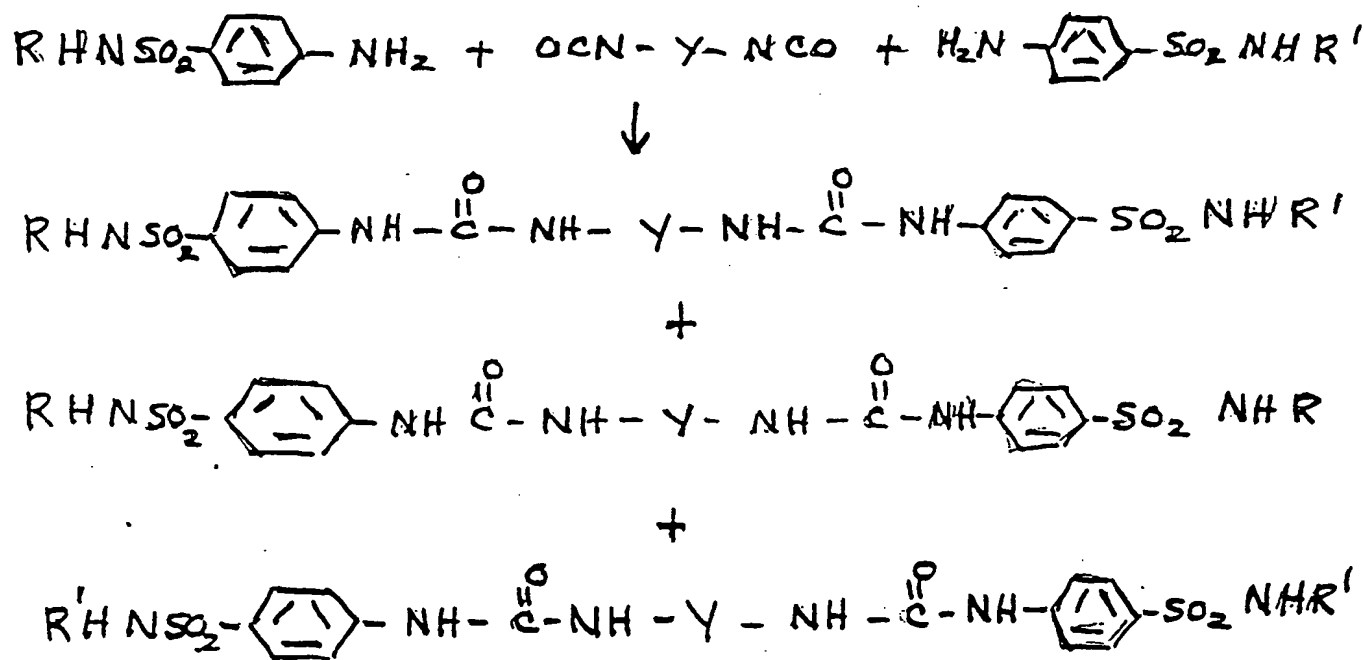


structures is the aromatic amino group. Consideration of the entire group of sulfonamides listed above will show that the only reactive group is the aromatic amino group. Of the five linking reagents listed above, four may be employed: diisocyanates, dianhydrides, diacidchlorides, and diepoxides.

The structures which result from coupling sulfonamides with sulfonamides are shown below.



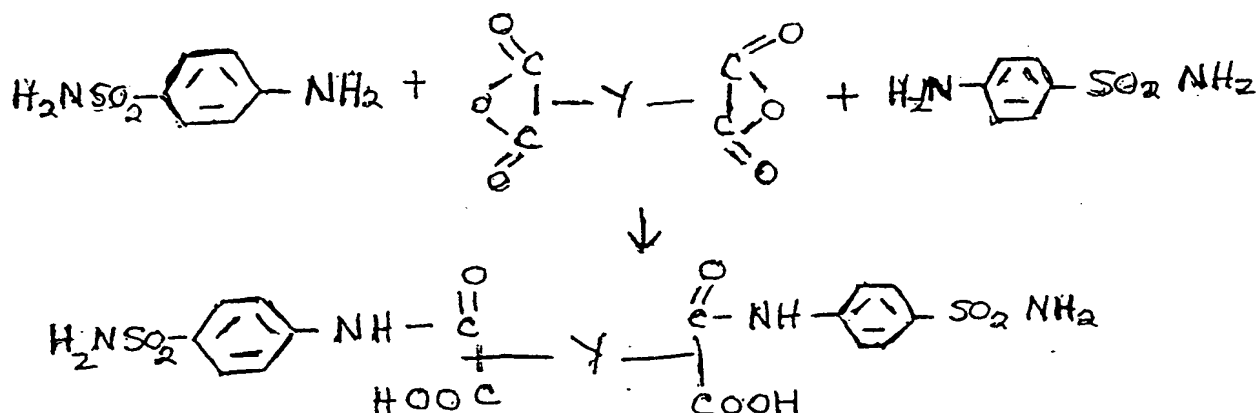
When identical sulfonamides are linked only a single product will result, but obviously when two nonidentical sulfonamides species are linked, three products will result as shown below.



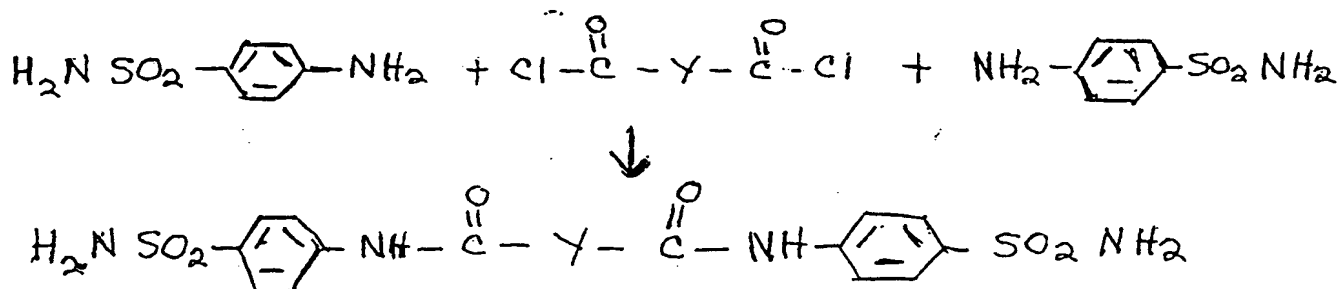
Since, in the experimental section below, equimolar quantities are used in all reactions the mixed products will predominate where the two reacting moieties have diverse structures. The modern methods of liquid chromatography render the separation of such simple mixtures, as above, to be quite simple, thus adequate material can be separated for microbial evaluation tests. Commercial quantities can be separated via preparative scale HPLC (high performance liquid chromatography).

The linking of two antibiotic moieties by utilizing dianhydrides follows a course identical to that described for diisocyanate linking agents, i.e., when a single type moiety is employed, a single product will result, but when two

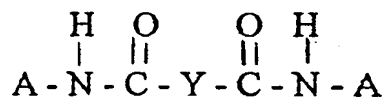
dissimilar moieties are employed, three products will result. As noted with diisocyanates, separation and evaluation of these products is not difficult.

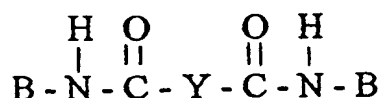
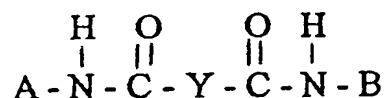


The linking of two antibiotic moieties utilizing diacid chlorides will pursue a course analogous to the reactions of diisocyanates. When a single antibiotic entity reacts with a diacid chloride a single entity results, but when two different entities react, three products are formed.

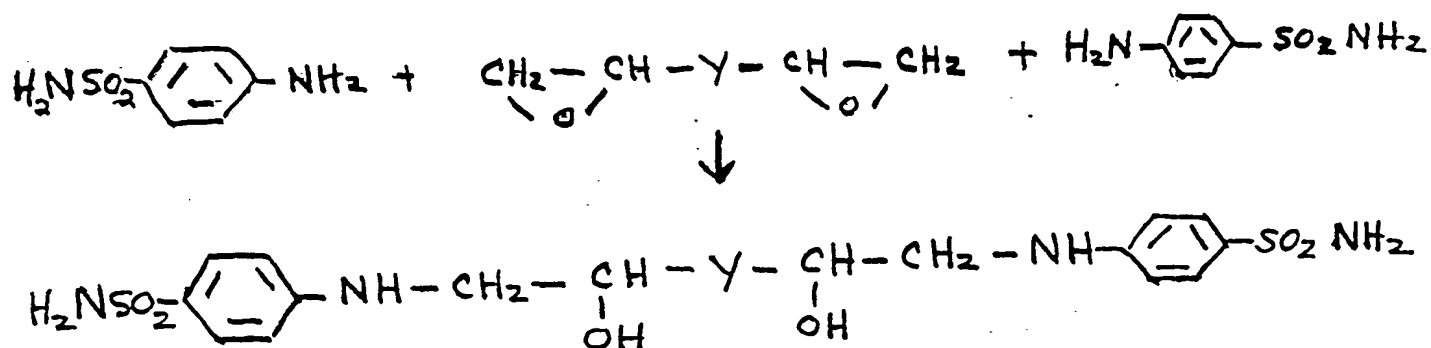


Symbolically, the three products can be seen as:

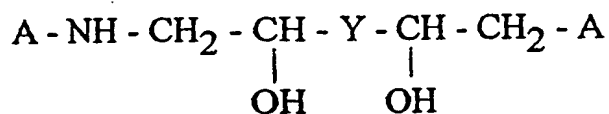
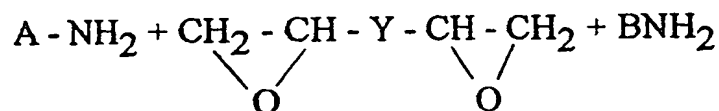


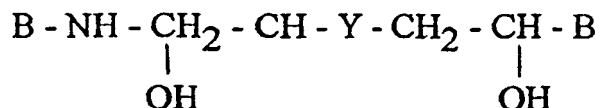
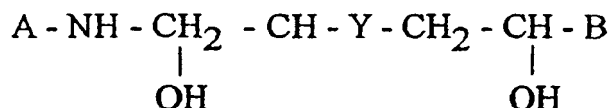


The reaction of two antibiotic moieties with a diepoxide follows a course similar to the diisocyanate reaction with a single moiety resulting in a single product and two moieties resulting in three products, as shown below.



It will be noted that in the ring opening reaction the attack occurs on carbon #1 in the epoxy group predominantly.

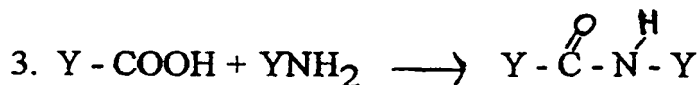
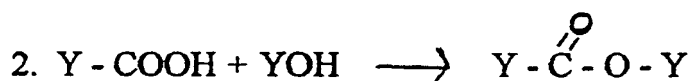


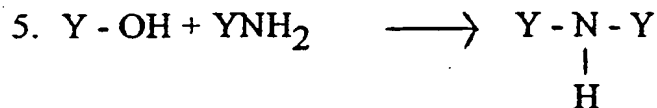


The above comments with respect to product mix apply to all antibiotic linking reactions occurring with the linking agents diisocyanates, dianhydrides, diacid chlorides, and diepoxides.

The use of the dicarbodiimides with antibiotic moieties follows a different pattern. The situation when linking antibiotic moieties via carbodiimides is the result of removing the elements of water from two moieties.

Thus the linking of two antibiotic moieties depends upon the presence of the following groups: carboxyl, amino and hydroxyl and requires a minimum total of two such groups, but with a further plurality may also be utilized. The possible combinations of the three reactive groups are five.

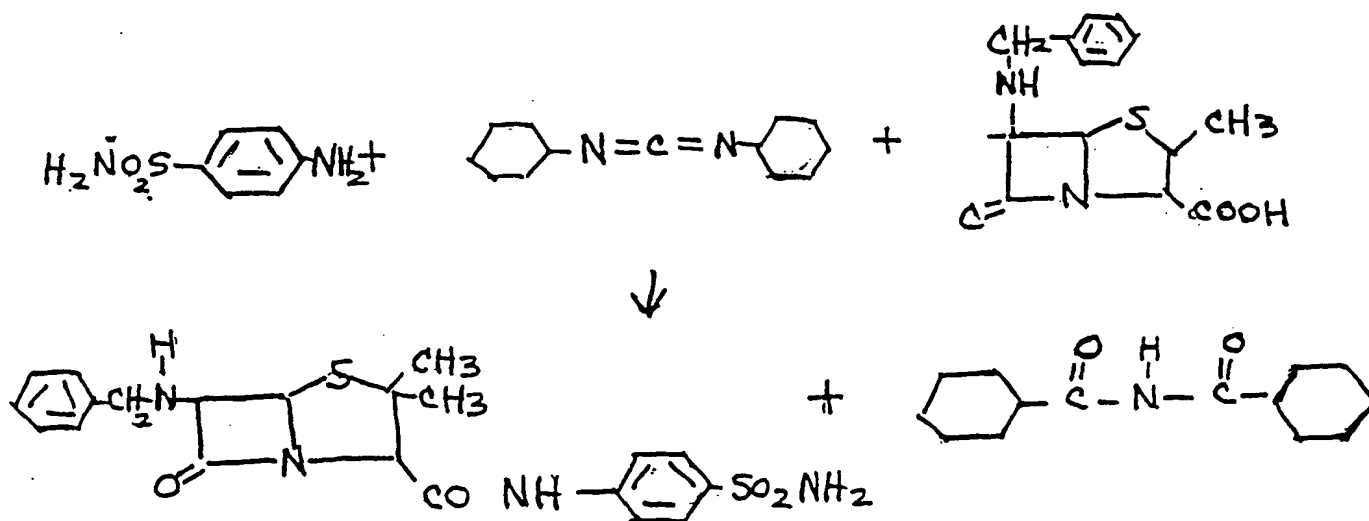




The linking of two antibiotic moieties via the groups above produces the following products:

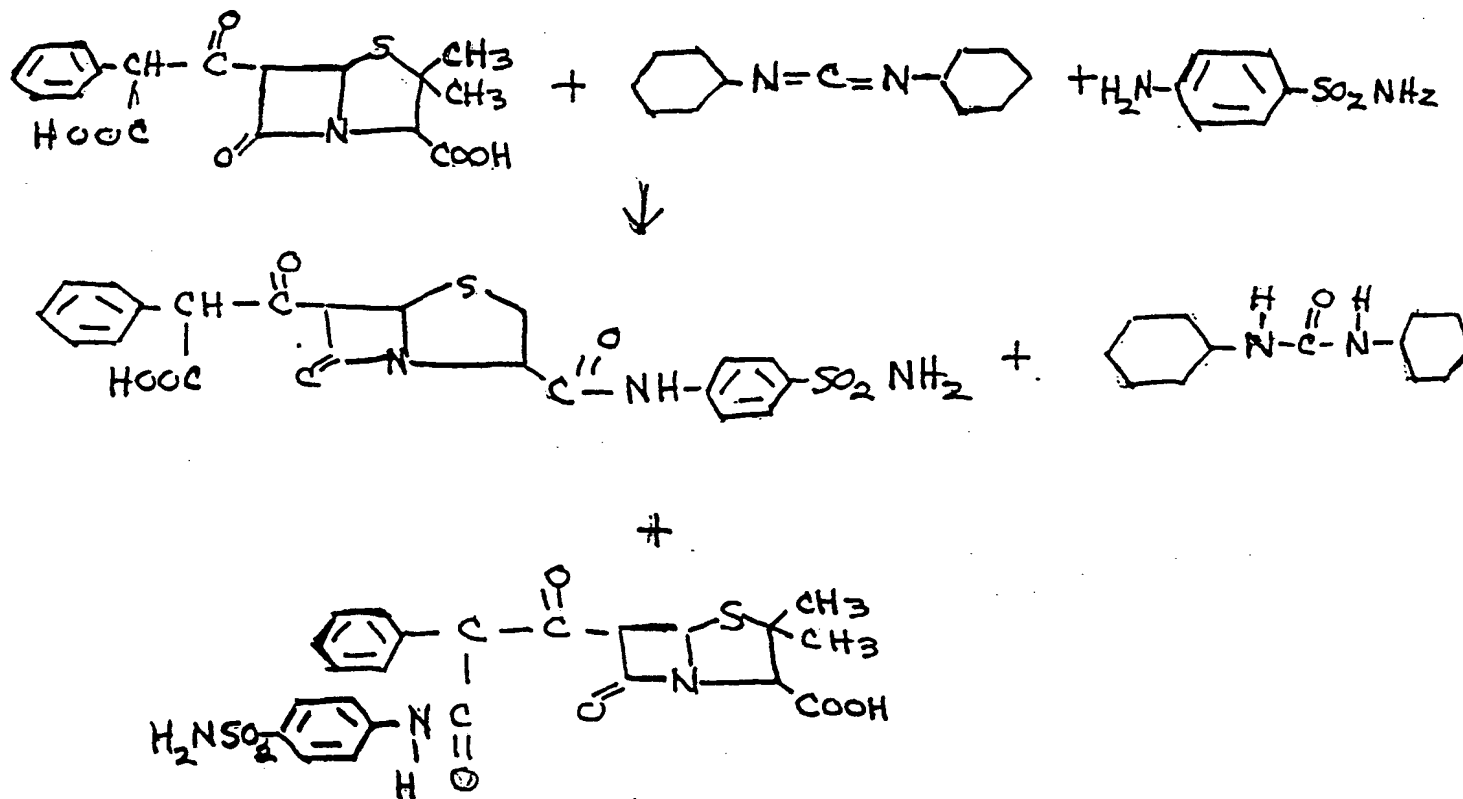
1. anhydride $\text{Y}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\overset{\text{O}}{\parallel}\text{C}-\text{Y}$
2. ester $\text{Y}-\overset{\text{O}}{\parallel}\text{C}-\text{O}-\text{Y}$
3. amide $\text{Y}-\overset{\text{O}}{\parallel}\text{C}-\text{NH}-\text{Y}$
4. ether $\text{Y}-\text{O}-\text{Y}$
5. amine $\text{Y}-\text{NH}-\text{Y}$

When two antibiotics are linked each containing a single reactive group, as one COOH and one NH₂, only a single product will result; see the example below of the reaction of dicyclohexylcarbodiimide with p-aminobenzenesulfonamide with benzylpenicillin.



The amide product is easily separated from the by-product dicyclohexylurea by crystallization or liquid chromatography techniques.

When more than two active groups are present on a single moiety as penicillin type, carbenicillin, two products will result when linked with p-aminobenzenesulfonamide via dicyclohexylcarbodiimide, as shown below.



Rules are developed in the "Rules" section below to account for all products with all linking reagents linking the many antibiotic moieties.

Linking Rules

The linking rules developed below are based on the interactions of the five linking agents with a large number of eight classes of antibiotics.

DESCRIPTION OF THE INVENTION

Section 3

The rules for linking the antibiotic moieties are developed by considering all of the above data just concluded for linking all of the individual members of the said eight groups of antibiotics.

The linking rules are as follows:

1. Diisocyanates can react with all acid carboxyl groups, all hydroxyl groups and all primary and secondary amino groups. Thus any antibiotic moiety containing a carboxylic acid group, a hydroxyl group or an amine group, can be linked to any other antibiotic moiety also containing a carboxylic acid group, hydroxyl or amine function.

When a single antibiotic moiety contains a plurality of groups, as a carboxyl group and a hydroxyl group, or a carboxyl group and an amino group, this moiety can be linked by reaction with a diisocyanate to a second antibiotic moiety containing a plurality of groups, as a carboxyl group and a hydroxyl group, or a carboxyl group and an amino group.

When a diisocyanate is utilized to link antibiotic moieties containing a plurality of carboxyl acid, alcohol and amino groups, a mixture of products will be realized, but with chromatographic techniques the mixtures are easily separated.

Summarizing: the diisocyanate reagent can be used to link any two antibiotic moieties each containing at least one carboxylic acid, alcohol or amino functional group, and can also be used when each antibiotic contains a plurality of said groups.

2. Dianhydrides can be utilized to link a wide variety of antibiotic moieties in which each moiety contains at least one hydroxyl or primary or secondary amine group. The dianhydride reagent can also be utilized to link antibiotic moieties in which each moiety contains a multiplicity of hydroxyl or amino groups. In cases involving the linking of antibiotic moieties containing a multiplicity of groups, a mix of products will be realized but can be separated easily via chromatographic techniques.

3. Diacidchlorides as a linking agent are covered by rules identical to those for dianhydrides. Diacidchlorides can be used to link a wide variety of antibiotic moieties in which each moiety contains at least one hydroxyl or amino group. The acidchloride reagent can also be used to link antibiotic moieties where each moiety contains a multiplicity of hydroxyl or and amino groups. In cases involving a multiplicity of groups, a mixture of products will be realized which can be separated easily via chromatographic techniques.

4. Diepoxides as linking agents can be used to link antibiotic moieties where each moiety contains a carboxyl, hydroxyl, or amino group, or where each moiety contains a plurality of said groups. When antibiotics possessing a plurality of such groups react with the epoxy linking agents a complex mix of products will be formed which can be separated via chromatographic techniques.

5. Carbodiimides as linking agents can be utilized to link a very large number of antibiotic types. Antibiotic moieties in which each moiety

contains a single carboxyl group yield anhydrides. Antibiotic moieties in which one moiety contains a carboxyl group only will react with a moiety containing a single hydroxyl group to form a single ester. Antibiotic moieties containing a plurality of carboxyl and hydroxyl groups will form a complex mixture of esters when reacted with carbodiimides. Antibiotic moieties containing a single carboxyl group will react with antibiotic moieties containing a single amino group to form a single product containing an amide group. When antibiotic moieties containing a multiplicity of carboxyl, hydroxyl and amino groups are linked via carbodiimides, a mixture of esters and amides will be formed. When antibiotic moieties containing singular hydroxyl groups or a multiplicity of hydroxyl groups are linked, the products will be singular or multicomponent ethers. The linking of antibiotic moieties containing singular or multiple hydroxyl and amino groups leads to the formation of a single substituted amine, or a multiplicity of amines. All of the mixtures generated by the above said reactions can be separated via chromatographic techniques.

DESCRIPTION OF THE INVENTION

Section 4

Experimental Procedures

General Comments - The procedures outlined and discussed below describe the experimental procedures necessary to carry out the linking procedures with the many antibiotic moieties previously described in this application.

Procedures for each linking reagent.

Coupling reactions using:

1. Diisocyanates:

Solvents	pyridine	50 ml	anhydrous
	DMAC	50 ml	anhydrous
	DMF	50 ml	anhydrous
	N-methylpyrrolidone	50 ml	anhydrous
Temperature	0 to 50°C		
Time	5-10 hours		
Quantities	0.01 mole each antibiotic moiety, 0.005 mole of linking reagent		
Monitor	via IR spectroscopy for -NCO group, 4.45 μ		
Work-up	add water to ppt. product		
	achieve separation of products via chromatography; TLC, column or HPLC.		
Evaluation	apply to streaked plate of several cultures--E. coli, Strep. Group A, P. aruginosa		

Equipment	250 ml round bottom 3-neck flask equipped with glascol mantle for heating, thermometer, reflux condenser and teflon stirring bar energized by magnetic stirring.
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Coupling reactions using:

2. Dianhydrides

Solvents	Same as "1".
Temperature	Same as "1".
Time	Same as "1".
Quantities	Same as "1".
Monitor	IR via 5.50 and 5.80 anhydride band
Work up	See 1.
Evaluation	See 1.

Coupling reactions utilizing:

3. Diacid chlorides*

All same as 1, but IR monitor via 5.80 acid chloride band in IR

*Prior to the addition of water to terminate the reaction g. (0.25 ml) of sodium bicarbonate is added in small portions to neutralize all hydrochloric acid.

Coupling reactions utilizing:

4. Diepoxides

All same as in 1, but reaction time may be extended to 24 hours to complete reaction. IR monitor via epoxide band at 9.5 μ .

Coupling reactions utilizing:

5. Carbodiimide

All same as 1, but reaction time may be as short as 1 hour. IR monitor is via carbodiimide band at 4.50μ .

Example procedure

1. The reaction p-aminobenzene sulfonamide with sulfapyridine.

The dry pyridine solvent, 50 ml., is placed in the 250 ml round bottom flask and 1.72 g. (0.01 mole) of p-aminobenzenesulfonamide and 1.68 g. (0.01 mole) of hexyldiisocyanate is added, the temperature raised to 40°C by means of the variac controlling the heating of the glascol mantle. The heating and stirring are continued for 4 hours, and at the end of each hour a small sample is withdrawn from the flask by means of a pippette and examined by means of IR spectroscopy. The IR spectroscopy scan is determined from 2.5 microns to 15.0 microns, and the concentration of diisocyanate is determined from the intensity of the absorption band at 4.45 microns, a band due to the -NCO group. A steady drop in the concentration of the -NCO group indicates progress of the reaction. At the end of 4 hours at 40°C the concentration of the isocyanate group has dropped by 80 per cent. The reaction is forced to conclusion by raising the temperature to 50°C for two hours, at the end of which time the -NCO group is not detectable by IR spectroscopy.

The reaction is terminated by the addition of 50 ml of water and the precipitated reaction product dried in a vacuum oven at 25°C for 2 hours to

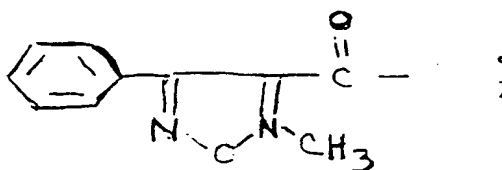
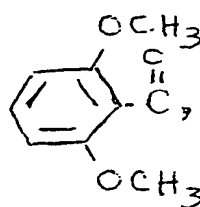
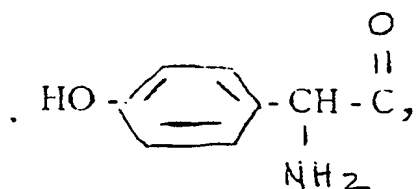
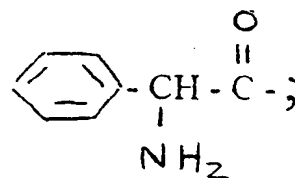
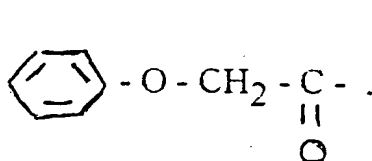
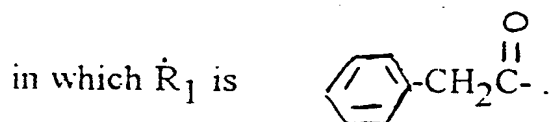
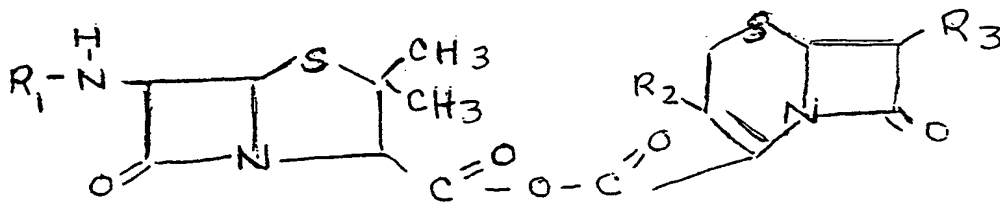
yield 3.0 g., 8.8 per cent. The product was evaluated for biological activity via applying a 1 per cent solution in pyridine to TLC (thin layer chromatography) plates. The developing solvent used was a 10-90 mixture of acetone and methanol, and the progress was monitored by a UV light. The spots on the chromatogram were evaluated via mechanical removal and the absorbent was separated from the product fraction by dissolving in pyridine, and the pyridine solution was dried onto filter paper. Tabs of the filter paper were applied to agar culture plates streaked with standard bacterial cultures of *S. aureus*, *E. coli* and *P. aureginosa*. Standard antibiotics, as p-aminosulfonamide and penicillins were used for comparison. All products showed modest inhibition zones in the vicinity of the filter paper tabs containing the product fractions.

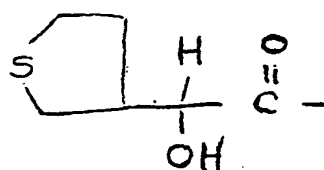
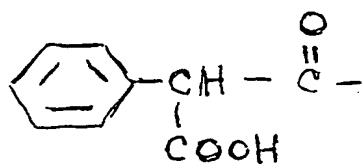
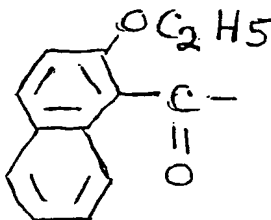
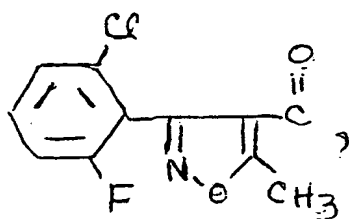
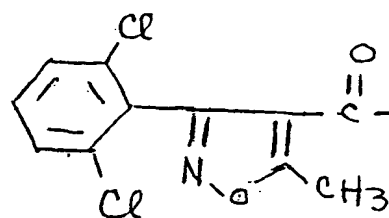
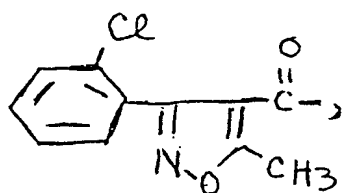
Larger quantities of products are obtainable for animal testing most simply via prep scale liquid chromatography.

CLAIMS

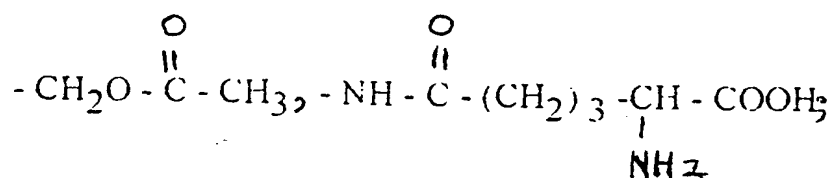
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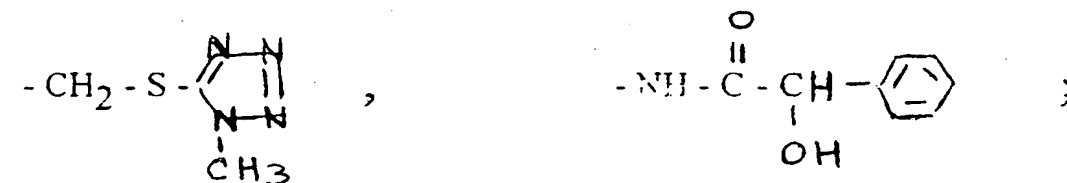
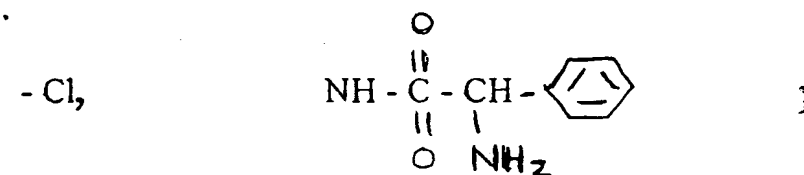
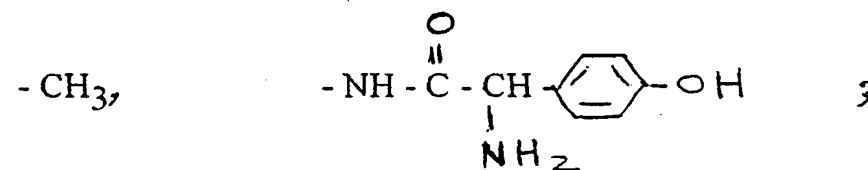
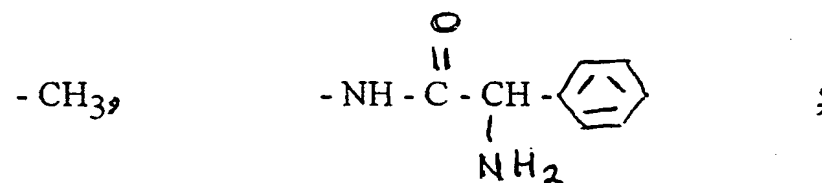
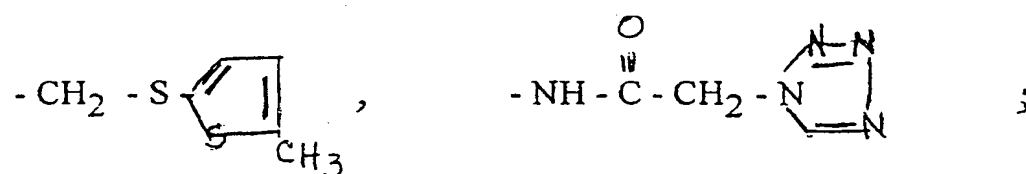
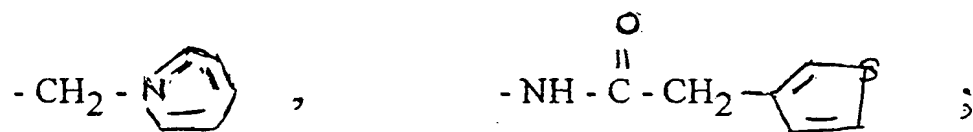
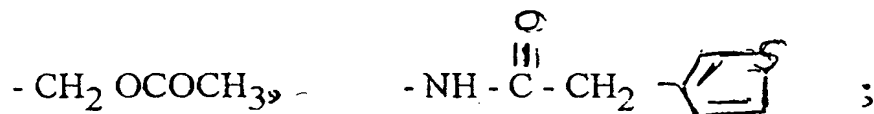
1. An acid anhydride of the formula

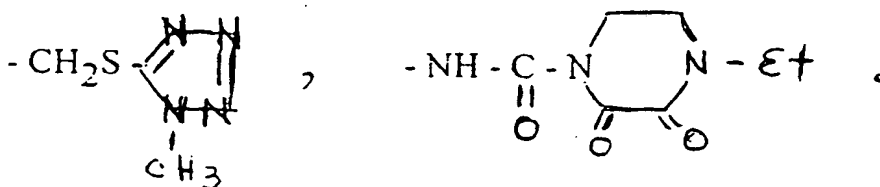
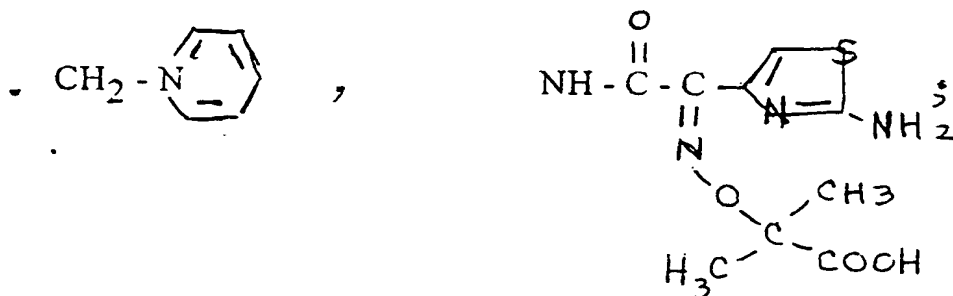
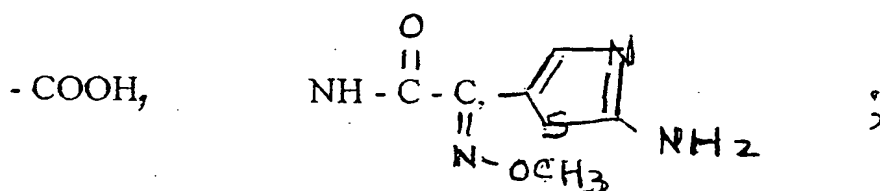
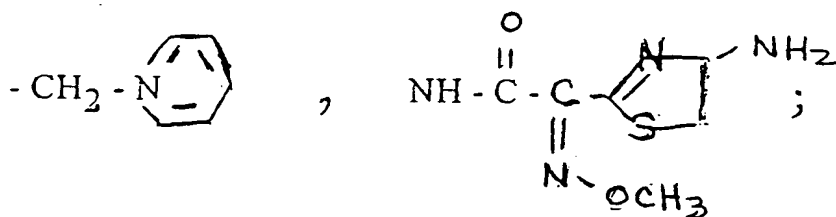
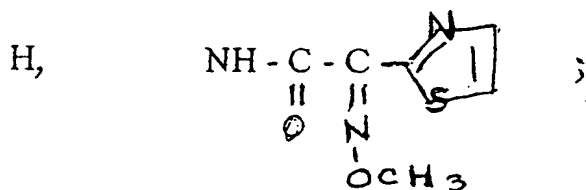
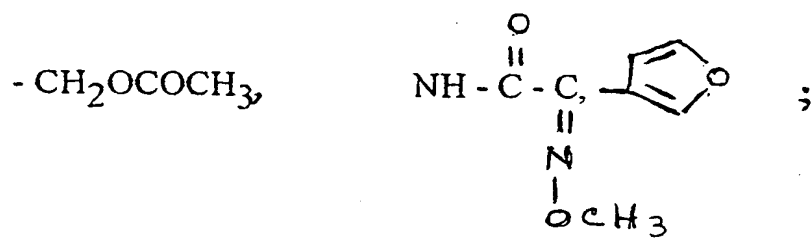




R_2 and R_3 are:

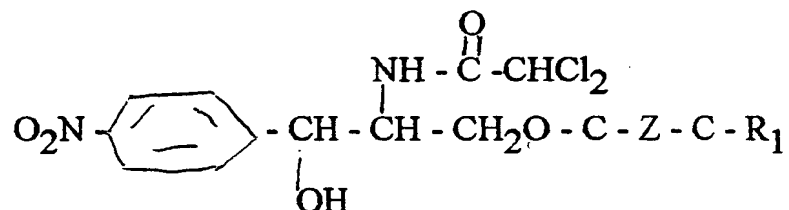






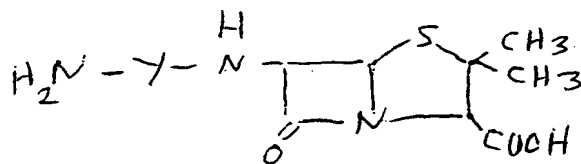
2. A process for preparing the compounds of Claim 1 by reacting a penicillin compound with a cephalosporin compound in the presence of dicyclohexylcarbodiimide in pyridine solution, and isolating the reaction product by means of liquid chromatography and identifying the reaction product by means of IR spectroscopy.

3. A compound of the general formula



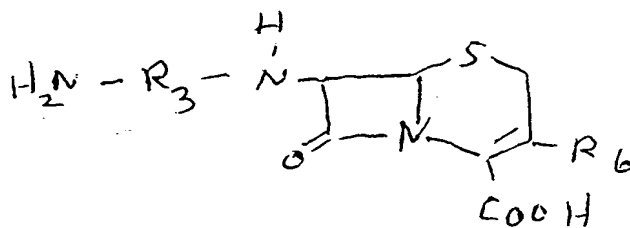
where Z is $(\text{CH}_2)_n$ wherein n is 2-20 methylene units and R_1 is one of the following groups of antibiotics

a) A beta-lactam of the general formula



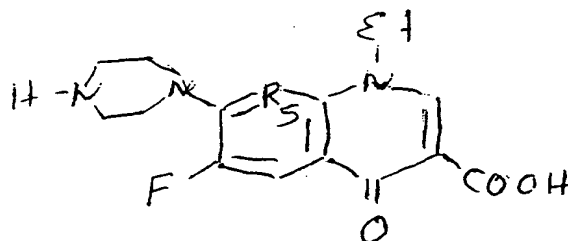
wherein Y is a side chain containing a pendant amino group;

b) A beta-lactam of the general formula, termed cephalosporin type,



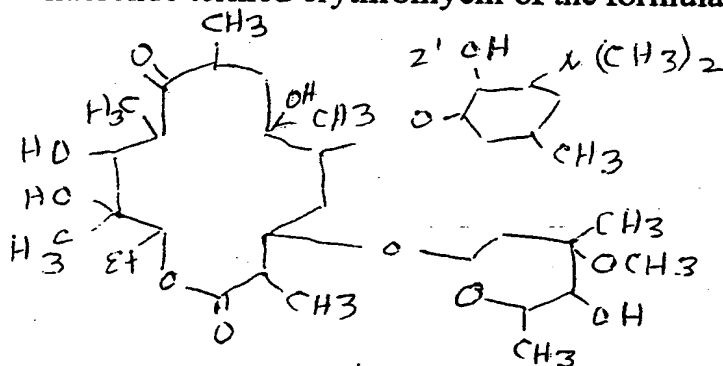
wherein the molecule contains a six-member sulfur-containing ring, R_2 is H, methyl or carboxyl, and R_3 is a complex side chain always carrying a pendant amine group;

c) A quinolone antibacterial of the general formula wherein



R_5 is a carbon or a nitrogen atom and the piperazinyl side-chain carries one free secondary amino group;

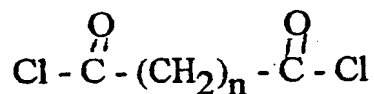
d) A macrolide termed erythromycin of the formula shown containing



a reactive hydroxyl in the 2'' position in the diisooamine portion of the erythromycin molecule; all said antibiotics being linked to chloramphenicol;

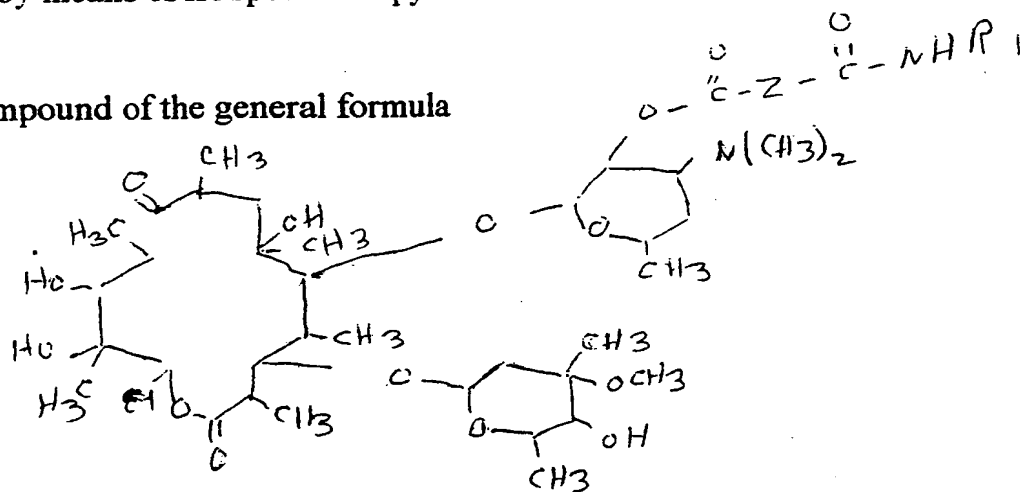
4. A process for the preparation of the compounds of Claim 3 by reacting 2,2-dichloro-N-[2-hydroxyl-1-hydroxymethyl-2-(4-nitrophenyl)ethyl]

acetamide with a penicillin, a cephalosporin, a quinolone and an erythromycin in the presence of a diacid chloride of the structure



wherein n is greater than 2 in pyridine solution and isolating the reaction product by means of liquid chromatography and identifying the reaction product by means of IR spectroscopy.

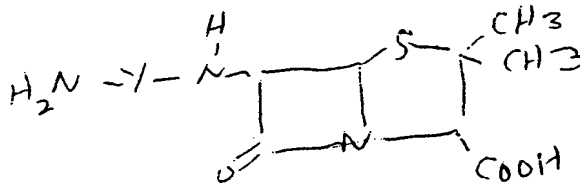
5. A compound of the general formula

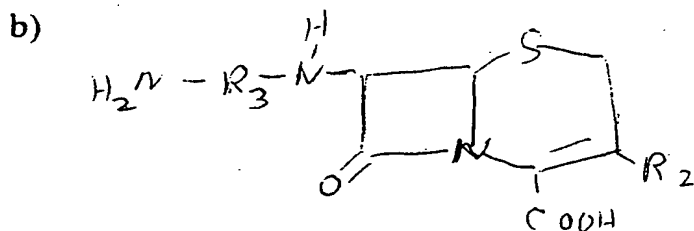


wherein Z is $(\text{CH}_2)_n$ wherein n is 2-20 and R_1 is one of the following groups of antibiotics

a) A beta-lactam of the penicillin type where Y is a side chain containing a pendant amino group

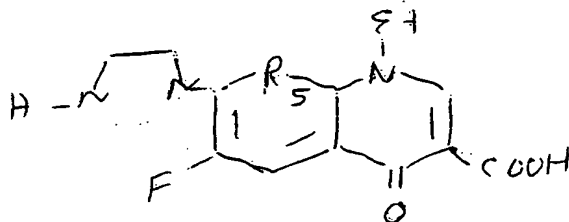
a)





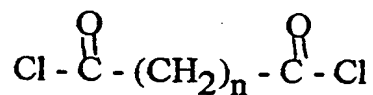
b) A beta-lactam of the cephalosporin type wherein the molecule contains a 6-membered ring containing sulfur, R_2 is a methyl, hydrogen or carboxyl group and R_3 is a complex side chain carrying one pendant primary amino group,

c) A quinolone antibacterial of the general formula



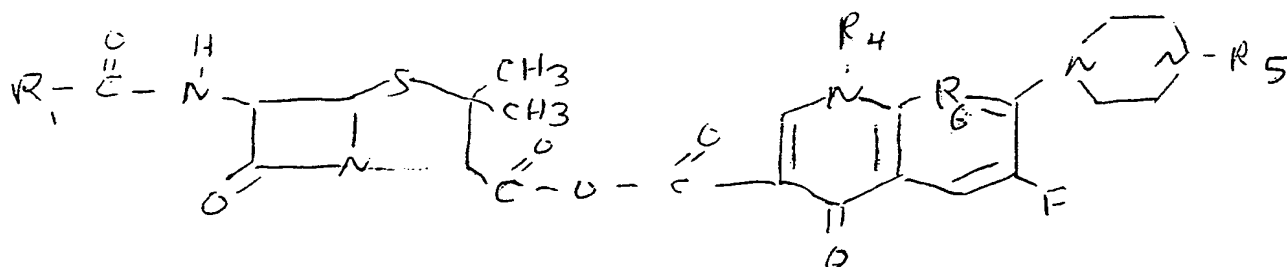
- wherein R_5 is a carbon or nitrogen atom and the piperazinyl side-chain carries one free secondary amino group.

6. A process for the preparation of the compounds of Claim 5 by reactioning erythromycin with a penicillin, a cephalosporin, and a quinolone in the presence of a diacid chloride, of the structure



wherein n is greater than 2, in pyridine solution and isolating the reaction product by means of liquid chromatography and identifying the reaction product by means of IR spectroscopy.

7. An acid anhydride of the formula



in which R_1 is equivalent to R_1 in Claim 1, and R_4 , R_5 , R_6 , are respectively

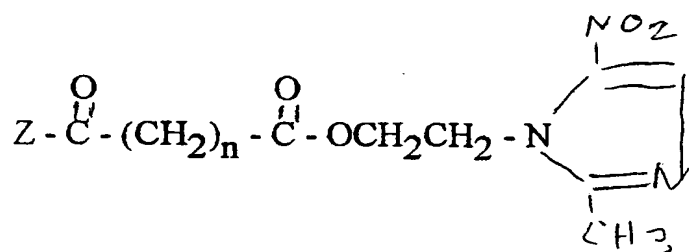
- Ethyl, - H, - C = ; Ethyl, H, N = ;

- cyclopropyl, H, = C - ;

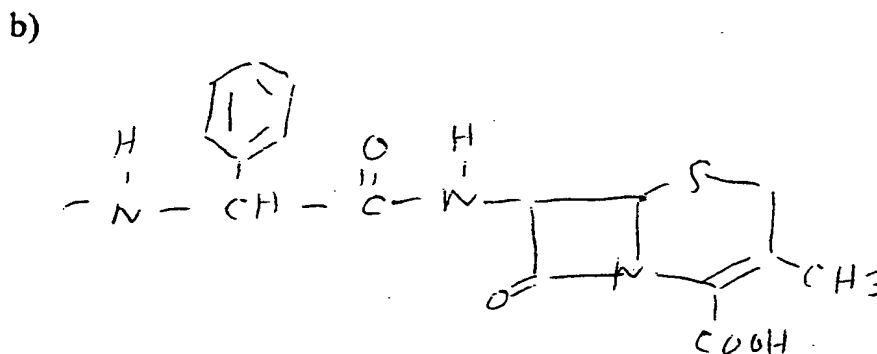
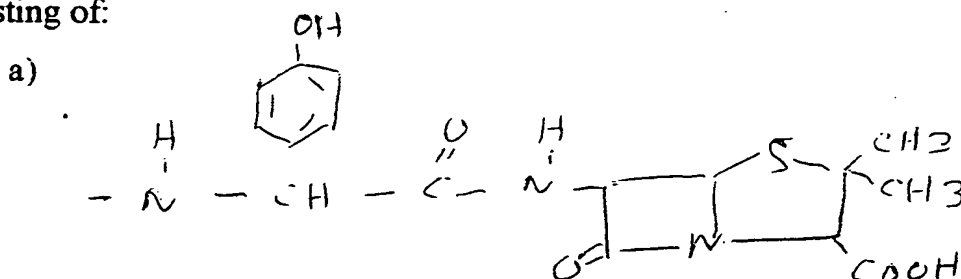
- $\text{C} = \text{C} - \text{O} -$, CH_3 , = C - O -
 CH_3

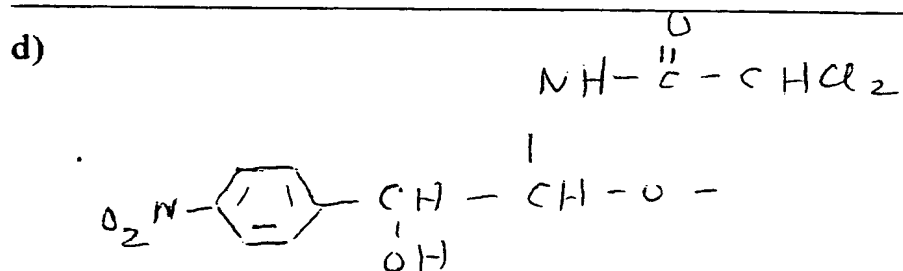
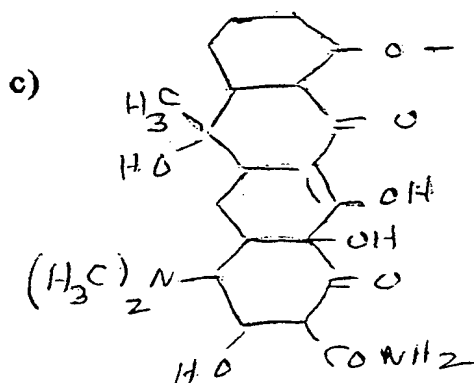
8. A process for the preparation of the compounds of Claim 7 by reacting a penicillin with quinolones in the presence of dicyclohexylcarbodiimide in pyridine solution and isolating the reaction product by means of liquid chromatography and identifying the reaction product by means of IR spectroscopy.

9. A pharmaceutical compound having the following formula

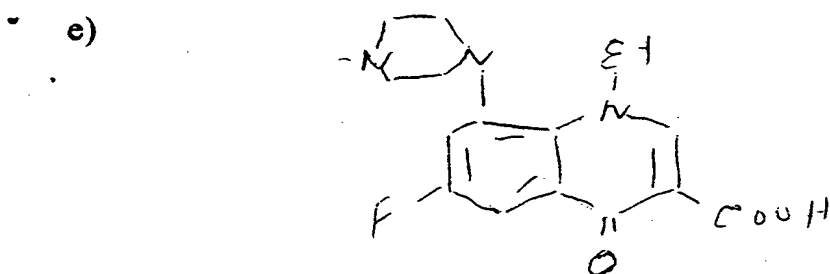


where "n" is an integer of 2-12; and where "Z" is selected from the group consisting of:



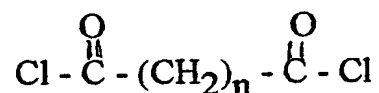


and



all antibiotic a - e being linked to 2-methyl-5-nitroimidazole-1-ethanol.

10. A process for the preparation of the compounds of Claim 7 by reaction of 2-methyl-5-nitroimidazole-1-ethanol with a penicillin, a cephalosporin, a tetracycline, chloramphenicol, and a quinolone in the presence of a diacid chloride,



wherein n is greater than 2 in pyridine solution and isolating the reaction product by means of liquid chromatography and identifying the reaction product by means of IR spectroscopy.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/22012

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 279/16. 417/00

US CL :544/50, 55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/50, 55

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 113, No.130724, 28 May 1990 (Columbus. OH, USA); KURODA, "MANUFACTURE OF CEPHALOSPORINS WITH PENICILLIN G AMIDASE". See abstract.	1-2
Y	Chem. abstr., VOL. 120, No. 293945, 1994 (Columbus OH), PAGE, "THE REACTION OF CEPHALOSPORINS WITH PENICILLIN-BINDING PROTEIN LB.GAMMA. FROM ESCHERCHIA COLI". See abstract.	1-2

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 JUNE 1998

Date of mailing of the international search report

15 JUL 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Washington, D.C. 20231

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Authorized officer

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Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22012

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/22012

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

- Group I, claim(s) 1 and 2, drawn to Anhydrides of Penicillin and/or Cephalosporin and process of making.
Group II, claim(s) 3 and 4 (in part), drawn to Anhydrides of Chloramphenicol and Penicillin and/or Cephalosporin and process of making.
Group III, claim(s) 3 and 4, (in part),
drawn to Anhydrides of Chloramphenicol and Quinoline and process of making.
Group IV, claims 3 and 4 (in part) drawn to Chloramphenicol and Erythromycin and process of making.
Group V, claims 5 and 6, (in part) drawn to Anhydrides of Erythromycin and Penicillin/ Cephalosporin and process of making.
Group VI, claims 5 and 6 (in part) drawn to Anhydrides of Erythromycin and Quinoline and process of making.
Group VII claims 7 and 8, drawn to Anhydrides of Penicillin and Quinoline and process of making.
Group VIII, claims 9 and 10, drawn to Anhydrides of Nitroimidazole and Penicillin/ Cephalosporin and process of making.
Group IX, claims 9 and 10 (in part), drawn to Anhydrides of Nitroimidazole and Tetracyclin and process of making.
Group X, claims 9 and 10 (in part), drawn to Anhydrides of Nitroimidazole and Chloramphenicol; and process of making.
Group XI, claims 9 and 10 (in part), drawn to Anhydrides of Nitroimidazole and Quinoline; and process of making.

The inventions listed as Groups I-XI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The core of the whole molecule in each group is chemically distinct from each other; Reference of one will not be reference to another.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The special technical feature resides in the combination of each individual antibiotic and the anhydride to which it is linked. Since the antibiotics are themselves known, they cannot be the special technical individually, only in combination. Since there are three significantly different anhydrides claimed and three different antibiotics (penicillin and cephalosporin are considered equivalent) claimed, this results in nine separate compounds each having no special technical feature in common with others.

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